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Archives OF INTERNAL MEDICINE

SEPTEMBER 1956

VOLUME 98 NUMBER 3

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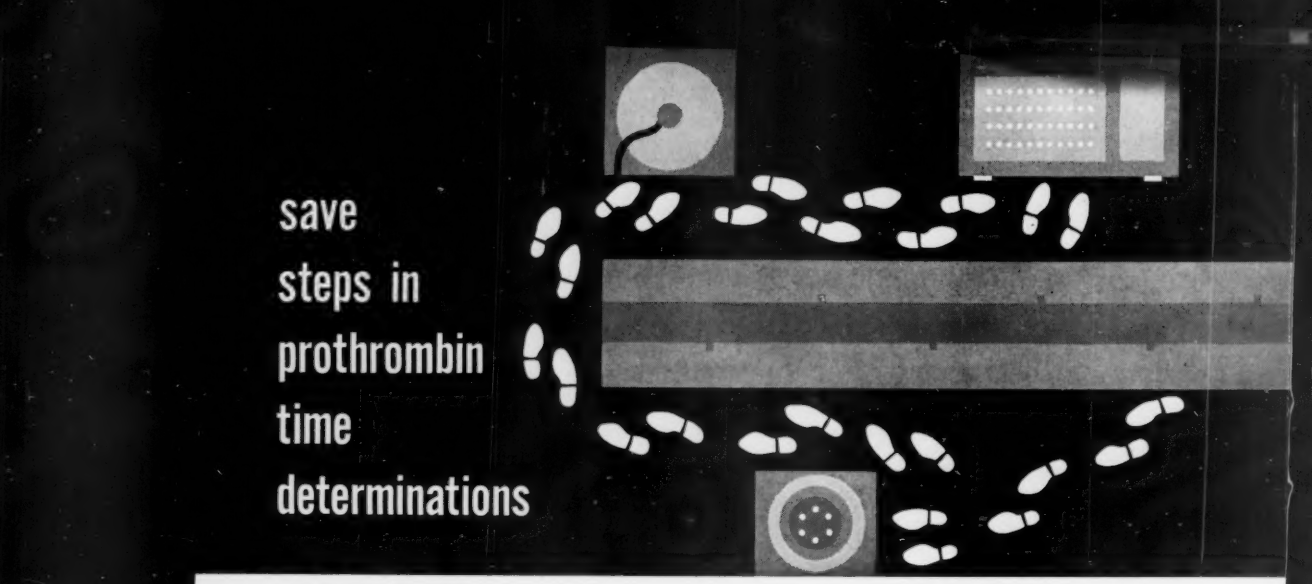

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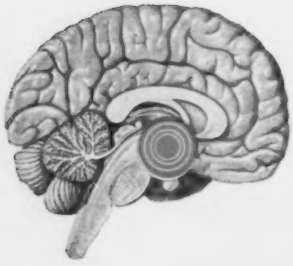

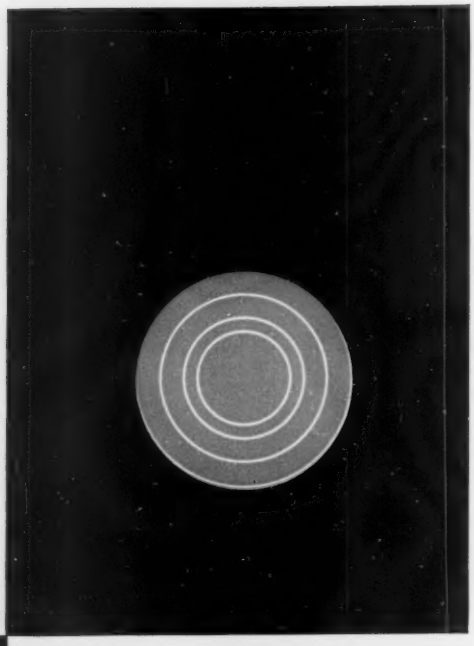

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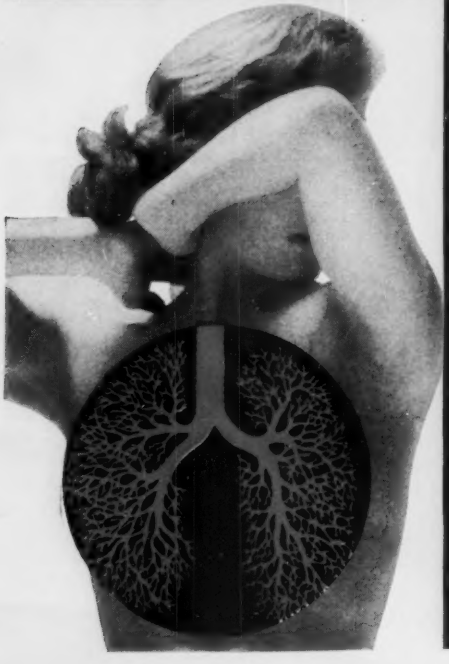

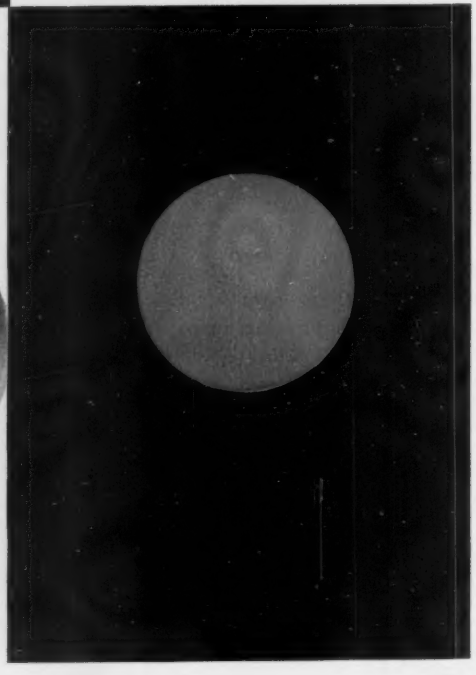

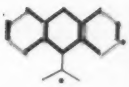

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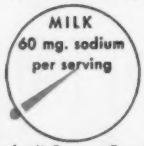

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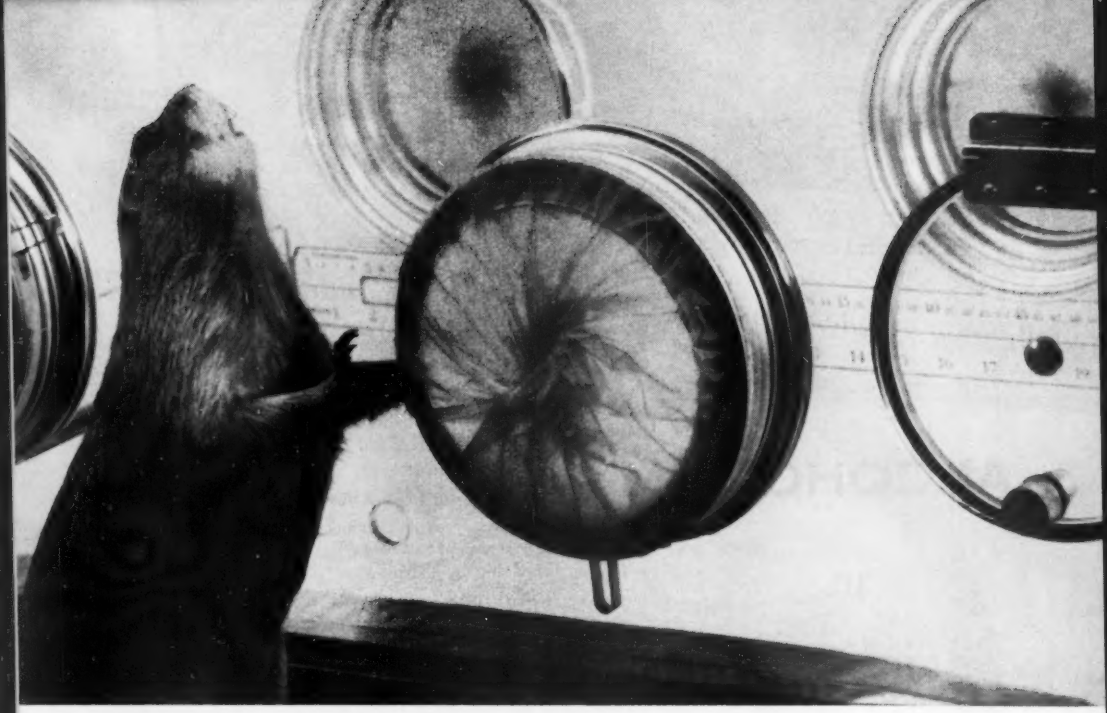

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References: 1. Hisaw, F. L.: Physiol. Zoöl. *2*:59 (Jan.) 1929. 2. Hisaw, F. L.; Meyer, R. K., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. *27*:400 (Feb.) 1930. 3. Hisaw, F. L., and Zarrow, M. X.: Vitamins & Hormones *8*:151, 1951. 4. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. & Metab. *14*:531 (May) 1954. 5. Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. & Metab. *15*:206 (Jan.) 1955. 6. Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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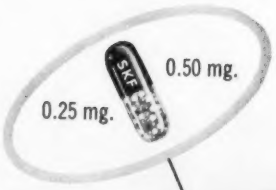

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Complete literature available on request.

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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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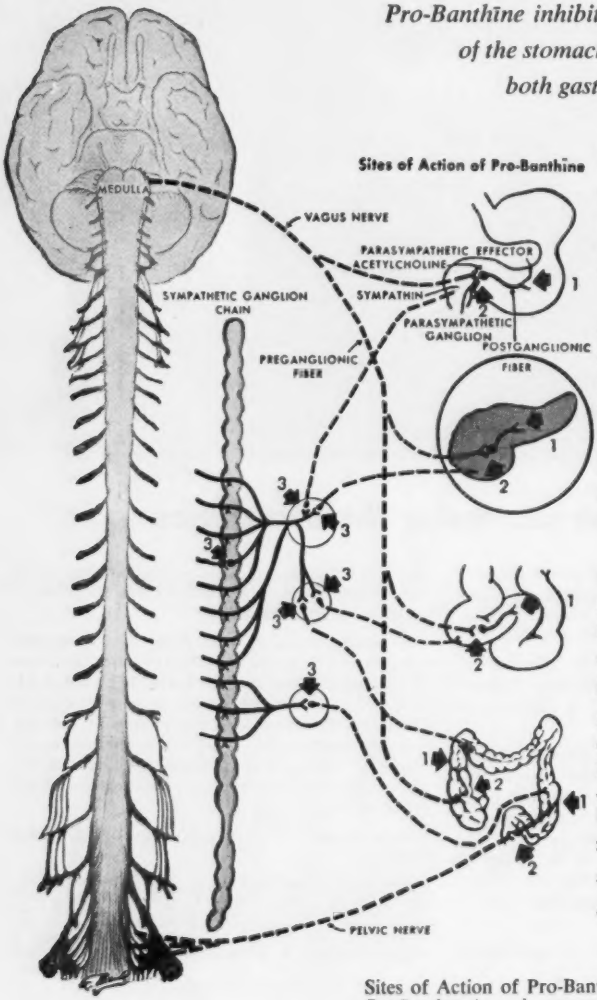

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1. Jones, C. A.: Arch. Int. Med. 96:332 (Sept.) 1955.
2. Zollinger, R. M.: Postgrad. Med. *15:* 323 (April) 1954.
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Evaluation of Adrenal Cortical Function by Stimulation with Corticotropin (ACTH)

NORMAN H. ENGBRING, M.D.
ROBERT B. TRUITT, M.D.
and
WILLIAM W. ENGSTROM, M.D., Milwaukee

Most tests previously employed to prove or disprove the presence of adrenal cortical insufficiency were, by their nature, indirect and depended on general metabolic or hematologic alterations which occur in the organism deficient in adrenal cortical hormones. Unfortunately, from a diagnostic point of view, the stress of nonspecific illnesses increases the demand for cortical hormone. False-positive water-loading tests and salt-deprivation tests are frequently seen in a variety of illnesses. Furthermore, the mere measure of the concentration of steroids in urine or blood frequently fails to differentiate those persons with adrenal insufficiency from those with intact adrenals. Apparently this is due to the considerable individual physiologic variations in excretion of steroid in health and in disease. To overcome this difficulty and still provide a direct and objective test of adrenal function, it is possible to combine the use of corticotropin (ACTH) with methods which measure the concentration of adrenal hormone. In this way the capacity of the adrenal cortex to respond to stimulation can be measured in a direct manner.

A technique commonly employed in clinical practice is that which involves the slow intravenous infusion of corticotropin in a dextrose solution, given over a period of 5 to 10 hours.[1] Administration of 20 to 25 U.S.P. units of corticotropin in this manner will evoke a maximal response in adrenal cortical function during the period of infusion, as reflected in the urinary steroid excretion.* A single infusion may be sufficient to establish the integrity of the gland; however, in some cases repeated infusions on three or more successive days may be necessary before an unequivocal rise in urinary steroids is observed.[2] Theoretically, it should be possible with corticotropin to stimulate any adrenal cortex to elaborate more hormone and to measure this increase. Even functionally atrophic glands should respond; only glands severely damaged by intrinsic disease should not respond. However, the technical difficulties which accompany prolonged intravenous infusion are quite apparent, and the degree of response of the adrenal cortex is frequently dependent upon the degree of cooperation of patient and personnel.

With the introduction of more uniformly potent preparations of repository corti-

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From the Department of Medicine, Marquette University School of Medicine and the Milwaukee County General Hospital.

This study was supported by funds from the United States Public Health Service and from the Milwaukee Chapter of the American Cancer Society.

* References 2 and 3.

cotropin injection, which can be given intramuscularly and which are capable of causing prolonged adrenal cortical stimulation,† a simpler technique became available. The results obtained from testing with these preparations were compared with those obtained with the intravenously administered corticotropin.

Materials and Methods

In each case urine was collected for two 24-hour periods to determine control values for 17-ketosteroids and corticosteroids. Thereafter, corticotropin was administered for three days. During this period, as well as the two following days, urine collections were continued and the steroid values compared with the controls.

For the intravenous method, 20 or 25 U.S.P. units of corticotropin was administered in a 5% dextrose solution over a period of five to six hours daily for three days.

For the intramuscular method 40 commercial units of the repository injection preparation (The Armour Laboratories, The Wilson Laboratories, or National Drug Company) was administered every 12 hours for three days. This relatively high dose was used in order to overcome the disadvantage of extravascular inactivation, although this has been a problem usually only when corticotropin has been administered over a prolonged period of time.

The 17-ketosteroids were determined by the Callow-Zimmerman method, using absolute alcohol and employing a color-correction equation.[4] Our range for normal healthy males is from 7 to 22 mg., and for females is from 5 to 17 mg. per 24 hours. The corticosteroids were determined by the sodium bismuthate method of Norymberski.‡ Sodium bismuthate converts most of the important urinary corticosteroids, in situ, to 17-ketosteroids.

† References 1 and 3.

‡ References 5 and 6.

TABLE 1.— *Record of Urinary 17-Ketosteroid Values of Thirty-Five Patients Who Were Given Intravenous Corticotropin* *

Patient	Diagnosis†	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
			1st	2d	3d	4th	5th			
J.G.	AS CVD	1.2	5.3	4.5	....	....	1.7	1	4.1	341
V.A.	Bronchiectasis	1.3	2.6	2.5	2.7	2.7	3.7	5	2.4	185
E.S.	Neurosis	1.5	2.0	1.0	4.7	0	1.7	3	3.2	213
A.J.	AS CVD	1.6	1.7	3.1	4.4	1.9	....	3	2.8	175
H.S.	Asthma	1.8	2.9	4.0	6.3	6.7	....	4	4.9	272
E.N.	Cirrhosis	1.9	2.3	2.8	3.0	2.9	3.1	5	1.1	58
F.B.	Carcinoma	2.1	1.6	4.5	4.9	4.4	1.7	3	2.8	133
A.V.	Rheumatoid arthritis	2.4	1.7	4.8	2.9	9.4	12.6	5	10.2	425
B.L.	Rheumatoid arthritis	2.4	3.0	4.6	4.4	3.7	....	2	2.2	92
R.B.	Hodgkins disease	2.5	3.4	2.0	3.9	....	....	3	1.4	56
H.H.	Pneumonia	2.5	5.8	7.9	9.3	2.5	5.0	3	6.8	272
R.M.	Cirrhosis	2.8	5.7	9.0	10.6	5.7	6.0	3	7.8	278
H.K.	Rheumatoid arthritis	3.1	2.6	3.4	5.8	3.9	4.1	3	2.7	87
F.K.	AS H CVD	3.5	8.4	15.1	10.9	14.3	9.2	2	11.6	332
H.D.	AS HD	3.6	4.0	8.6	7.1	5.9	....	2	5.0	139
O.J.	Dermatitis	3.6	9.1	7.9	10.0	4.7	3.0	3	6.4	178
W.R.	Rheumatoid arthritis	3.8	6.8	6.3	10.7	7.1	9.2	3	6.9	182
C.S.	Cirrhosis	4.2	4.7	7.4	7.4	7.6	3.8	4	3.4	81
J.B.	AS CVD	4.3	7.0	7.2	5.9	6.4	4.8	2	2.9	68
E.B.	Neurosis	4.4	10.8	8.4	13.5	9.9	....	3	9.1	207
M.W.	Dermatitis	4.9	6.0	7.2	6.9	6.1	4.4	2	2.3	47
H.G.	Carcinoma	4.9	8.7	7.6	3.2	1.4	1.6	1	3.8	78
L.S.	Cholecystitis	5.0	4.3	9.7	21.0	8.3	2.2	3	16.0	320
W.V.	Alcoholism	5.1	3.2	5.9	3.2	8.3	....	4	3.2	63
G.O.	Dermatitis	5.1	4.9	6.2	4.7	3.6	....	2	1.1	22
P.Z.	Grave's disease	5.7	5.0	8.9	9.1	6.7	4.0	3	3.4	60
C.C.	CVA	6.1	17.5	16.9	19.0	3.6	6.6	3	12.9	212
M.H.	H CVD	6.4	10.9	14.8	20.0	16.4	7.7	3	13.6	212
R.H.	Asthma	7.9	10.5	19.7	31.5	14.3	7.1	3	23.6	299
A.J.	Infectious polyneuritis	8.0	8.9	10.4	13.7	9.1	7.0	3	5.7	71
L.C.	Diabetes	10.1	12.1	15.4	16.3	8.3	7.9	3	5.3	53
H.A.	Hepatitis	10.9	15.1	22.0	19.9	19.2	13.0	2	11.1	102
J.U.	Rheumatoid arthritis	12.9	23.7	23.5	26.7	9.9	8.5	3	13.8	107
H.E.	Meningitis	13.1	16.2	20.8	28.3	14.1	11.5	3	15.7	120
R.G.	Alcoholism	19.2	22.7	26.2	28.9	15.5	14.0	3	9.7	51
Average		5.1	7.5	9.4	12.3	7.4	6.1		6.8	160

* The control value is an average of 2 days' collections. On the 1st, 2d, and 3d days 20 or 25 units of corticotropin was administered intravenously in 1000 cc. of 5% dextrose in water over a period of 5 to 6 hours. The last two columns show the maximum increase in milligrams and in per cent as compared with the control values.

† AS CVD indicates arteriosclerotic cardiovascular disease; AS HD, arteriosclerotic heart disease; H CVD, hypertensive cardiovascular disease; AS H CVD, arteriosclerotic hypertensive cardiovascular disease; CVA, cerebrovascular accident.

TABLE 2.—*Record of Urinary Corticosteroid Values (Milligrams per Twenty-Four Hours) of Thirty-Five Patients Given Intravenous Corticotropin* *

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
J.G.	85	F	3.8	9.5	15.4	----	----	2.1	2	11.6	306
V.A.	73	M	2.8	4.9	7.7	13.7	7.2	3.2	3	10.9	390
E.S.	31	F	4.1	5.3	3.6	15.0	2.6	2.0	3	10.9	266
A.J.	60	F	1.4	2.4	4.1	9.8	3.4	----	3	8.4	600
H.S.	74	M	0.6	1.0	1.5	2.7	2.5	----	3	2.1	350
E.N.	58	M	2.2	6.4	4.2	7.7	3.2	4.7	3	5.5	250
F.B.	66	M	3.4	1.0	5.2	0.6	10.7	5.1	4	7.3	214
A.V.	67	F	4.9	4.4	13.3	13.3	10.8	5.6	3	8.4	171
B.L.	46	F	3.2	5.8	9.6	16.6	4.5	----	3	13.4	419
R.B.	45	F	2.1	1.9	1.3	6.4	----	----	3	4.3	204
H.H.	53	M	2.5	4.4	2.6	10.6	2.8	6.3	3	8.1	324
R.M.	45	M	5.3	6.1	18.7	23.6	10.1	5.0	3	18.3	346
H.K.	31	F	3.8	5.1	10.1	19.0	12.2	5.8	3	15.2	400
F.K.	66	M	3.6	32.1	45.7	21.0	23.1	9.9	2	42.1	1,170
H.D.	68	M	1.8	1.8	19.9	27.2	9.6	----	3	25.4	1,410
O.J.	42	F	6.1	8.9	11.7	15.2	7.7	7.9	3	9.1	149
W.R.	48	M	3.2	9.4	6.0	15.8	11.5	5.8	3	12.6	394
C.S.	40	M	3.6	6.4	10.1	14.7	8.3	4.7	3	11.1	308
J.B.	75	M	5.9	7.5	11.0	8.4	5.6	1.6	2	5.1	86
E.B.	45	M	4.0	14.2	18.9	25.2	7.6	----	3	21.2	530
M.W.	73	M	4.2	8.6	10.1	15.6	7.9	3.4	3	11.4	272
H.G.	55	F	3.6	20.5	27.3	12.5	2.5	3.3	2	23.7	659
L.S.	57	F	3.8	9.2	25.2	49.6	11.1	2.6	3	45.8	1,200
W.V.	35	M	1.6	8.7	4.7	3.0	7.9	----	1	7.1	444
G.O.	17	F	2.7	6.0	22.6	23.1	9.5	----	3	20.4	756
P.Z.	51	M	5.1	3.2	4.5	11.5	5.0	1.1	3	6.4	125
C.C.	43	F	2.3	15.3	16.9	18 6	5.1	5.8	3	16.3	710
M.H.	72	F	6.1	17.7	12.8	8.8	49.3	19.0	4	43.2	709
R.H.	59	M	8.9	29.4	36.3	89.2	17.3	10.4	3	80.3	902
A.J.	15	M	4.6	12.7	30.2	17.5	12.9	8.2	2	25.6	558
L.C.	22	M	3.6	6.5	3.6	2.7	3.6	2.9	1	2.9	81
H.A.	36	M	7.9	8.8	28.8	20.8	0	11.6	2	20.9	264
J.U.	52	M	4.5	11.9	7.6	5.3	2.8	4.5	1	7.4	164
H.E.	37	M	9.6	5.8	18.1	13.3	10.8	7.8	2	8.5	89
R.G.	26	M	8.9	9.9	----	37.2	15.0	12.7	3	28.3	318
Average			4.2	8.9	13.8	17.5	9.2	6.0		17.1	441

* Determinations were made simultaneously with the previously charted 17-ketosteroid determinations.

The latter can be hydrolyzed, extracted, and assayed in the usual manner. This method is convenient and satisfactory for comparing changes in excretion in the same patient from day to day. Our range of normal is rather wide, being from 0 to about 10 mg. per 24 hours. No use was made of circulating eosinophile counts or the uric acid/creatinine ratio as indicators of adrenal cortical activity, since, because of their variability, it was felt that they would add little to the interpretation of the results.

Intravenous corticotropin was given to 35 patients and the long-acting intramuscular corticotropin to 22 patients. Their ages ranged from 15 to 85 years. Thirty-five were males, and twenty-two were females. The major diagnoses included a variety of acute and chronic illnesses, as indicated in Tables 1-4. Most of the patients were persons who suffered from chronic illnesses of moderate or severe nature. In a few instances the studies were done to exclude a diagnosis of Addison's disease which had been suspected from clinical or other laboratory evidence; further follow-up disproved the existence of adrenal insufficiency. Some of the tests were done to determine the response in patients with relatively acute or self-limited disorders. Since patients with acute, and especially those with chronic, illnesses are those which cause the greatest difficulty in excluding adrenal cortical insufficiency, and since in these the urinary steroid excretion is frequently depressed, it was felt that control studies should be performed on sick patients rather than on normal healthy persons.

For comparison, similar tests were carried out on four patients with Addison's disease and six patients with anterior pituitary insufficiency.

Results

The results of each test on the patients without adrenal or pituitary disease are individually recorded in Tables 1 through 4. The control figure is an average derived from two days' urine collections. The final two columns denote the maximum increase in 17-ketosteroid or corticosteroid values in milligrams and in per cent. A blank space in the charts indicates a mishap in the handling of the urine specimen for that day; however, the case was included in the series, since a definite response could be established from the other determinations. In

TABLE 3.—*Record of Urinary 17-Ketosteroid Values of Twenty-Two Patients in Milligrams per Twenty-Four Hours* *

Patient	Diagnosis	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
			1st	2d	3d	4th	5th			
H.K.	Paraplegia	0.6	0.6	1.0	3.7	----	----	3	3.1	517
B.M.	Arteriosclerotic cardiovascular disease	1.2	1.2	1.6	4.5	1.0	3.2	3	3.3	272
W.B.	Carcinoma	1.4	2.0	3.0	6.6	3.0	1.0	3	5.2	372
M.R.	Tuberculosis	1.5	1.9	2.3	4.3	3.9	----	3	2.8	186
A.B.	Asthma	1.8	2.0	5.1	3.3	6.1	2.8	4	4.3	239
J.J.	Diabetes	2.0	1.2	4.5	9.3	7.0	4.1	3	7.3	365
G.P.	Hip fracture	2.2	3.9	5.6	13.6	14.9	7.5	4	12.7	577
M.M.	Asthma	2.2	5.0	7.7	6.4	7.4	----	2	5.5	250
M.B.	Cardiovascular accident	3.0	3.5	8.3	6.2	6.3	----	2	5.3	178
N.D.	Neurosis	3.2	6.4	11.8	9.8	12.9	3.1	4	9.7	303
H.G.	Osteomyelitis of toe	3.5	4.9	4.6	6.3	5.2	6.7	5	3.2	91
V.N.	Carcinoma	3.8	11.3	15.3	14.4	4.6	4.5	2	11.5	302
C.K.	Tuberculosis	4.2	4.0	5.8	8.3	8.8	4.0	4	4.6	109
J.J.	Leg fracture	4.4	6.0	8.3	8.8	6.2	4.7	3	4.4	100
P.K.	Osteoarthritis	4.5	8.6	12.6	23.5	20.1	21.8	3	19.0	423
J.S.	Cirrhosis	5.4	6.0	5.2	10.1	5.0	4.3	3	4.7	87
E.D.	Pneumonia	5.8	8.8	7.4	9.9	7.2	7.9	3	4.1	70
R.T.	Rheumatoid arthritis	6.3	8.6	9.7	20.2	14.6	8.1	3	13.9	221
W.A.	Osteoarthritis	6.3	10.4	15.7	19.8	7.8	4.2	3	13.5	214
B.S.	Poliomyelitis	6.9	8.1	23.9	25.3	6.4	8.5	3	18.4	266
J.B.	Hepatitis	7.4	10.8	20.1	16.5	16.5	19.2	2	12.7	171
B.R.	Epilepsy	7.7	8.6	15.4	26.4	21.1	6.8	3	18.7	243
Average		3.9	5.6	8.9	11.7	8.9	6.8		8.5	252

* The control value is an average of 2 days' collections. On the 1st, 2d, and 3d days, 40 mg. of repository corticotropin injection was administered intramuscularly twice daily. The last two columns show the maximum increase in milligrams and in per cent as compared with the control value.

evaluating responses, the per cent increase was considered more important than the actual increment in milligrams. In all but three cases this was greater than 100% for either ketosteroid or corticosteroid values and when dealing with very low initial values (less than 2.0 mg.) was greater than 200%. Two of the patients who had poor responses (J. B. and L. C.) received intravenous corticotropin and showed maximal increases in 17-ketosteroids of 68% and 53% and in corticosteroids of 81% and 86% (Tables 1 and 2). The third (J. S.) received intramuscular corticotropin and showed a maximal 17-ketosteroid increase of 87% and corticosteroid increase of 95%.

An insignificant increase was much more frequently observed with the urinary 17-ketosteroids than with the urinary corticosteroids. Increments in 17-ketosteroid excretion of less than 100% were seen in 14 of the 35 patients given intravenous corticotropin and in 3 of the 22 patients given intramuscular repository corticotropin injection. An inconclusive rise in 17-ketosteroid values was almost invariably associated with a concomitant significant increase in corticosteroid values. The reverse was true in a few instances, although the corticosteroid response proved to be the more sensitive measure of adrenal cortical activity. This has been noted by other in-

TABLE 4.—*Record of Urinary Corticosteroid Values in Milligrams per Twenty-Four Hours on the Twenty-Two Patients Given Intramuscular Repository Corticotropin Injection* **

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
H.K.	53	F	4.8	3.5	5.9	22.6	----	----	3	17.8	368
B.M.	65	M	4.2	2.8	6.8	21.0	4.9	3.0	3	16.8	400
W.B.	63	M	1.7	8.8	28.1	40.8	10.2	3.9	3	39.1	2,300
M.R.	50	M	1.9	1.4	1.8	3.7	5.0	----	4	3.1	163
A.B.	21	M	1.0	3.2	10.9	8.9	7.6	5.2	2	9.9	990
J.J.	73	F	5.8	4.9	22.2	47.2	32.5	23.9	3	41.4	713
G.P.	76	M	2.2	4.7	7.2	34.5	5.5	14.0	3	32.3	1,470
M.M.	49	M	1.3	3.8	0.8	4.6	2.4	----	3	3.3	246
M.B.	66	M	1.7	11.0	8.9	5.4	10.1	----	1	9.3	546
N.D.	67	F	4.5	2.9	5.2	6.8	2.4	3.6	3	2.3	51
H.G.	55	M	1.2	4.6	5.0	6.9	4.9	4.8	3	5.7	475
V.N.	46	F	4.2	6.3	5.4	23.4	4.5	1.5	3	19.2	458
C.K.	65	M	6.0	5.1	10.4	27.3	13.5	9.6	3	21.3	355
J.J.	63	M	2.9	4.9	19.4	22.2	12.6	8.3	3	19.3	666
P.K.	52	F	5.2	24.8	7.4	41.0	6.8	19.4	3	35.8	689
J.S.	48	M	1.9	3.7	2.0	2.5	0.7	3.6	1	1.8	95
E.D.	61	M	9.7	10.9	12.2	21.2	11.0	13.1	3	11.5	118
R.T.	42	F	2.2	1.6	3.5	8.4	2.8	3.4	3	6.2	282
W.A.	57	M	3.0	23.0	40.4	43.3	9.1	2.4	3	40.3	1,340
B.S.	24	F	1.0	3.4	0.1	0.0	9.3	5.9	4	8.3	830
J.B.	19	F	2.6	13.3	12.7	13.0	16.5	10.6	4	13.9	535
B.R.	44	F	10.0	4.7	24.8	5.2	37.2	2.6	4	27.2	272
Average			3.6	7.0	11.0	18.6	10.0	7.7		17.5	607

* These determinations were made simultaneously with the previously charted 17-ketosteroid determinations.

vestigators.§ In the control group of 35 patients given intravenous corticotropin, the increase in corticosteroids was greater than the increase in 17-ketosteroids in 31 cases, and in the group of 22 patients given intramuscular corticotropin, the corticosteroid increase was greater in 17 cases.

The maximal increment in steroid excretion usually occurred on the third day of corticotropin administration, whether given intravenously or intramuscularly (Tables 1-4). Exceptions were noted, however, and for unknown reasons the maximal rise was observed on the first or second day of corticotropin administration and rarely immediately after it was discontinued. In these studies, a three-day period of corticotropin administration almost invariably produced

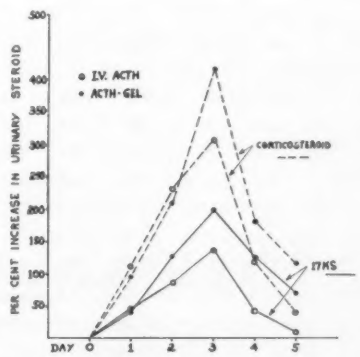

Fig. 1.—Average daily increments in urinary 17-ketosteroids and corticosteroids when corticotropin was administered on Days 1, 2, and 3. None of these patients had known pituitary or adrenal disease.

results adequate for diagnostic purposes. Even one or two days of corticotropin was

§ References 3, 6, and 7.

TABLE 5.—*Record of Twenty-Four-Hour Urinary 17-Ketosteroid Values of Four Patients with Anterior Pituitary Insufficiency Showing Response to Intravenously Administered Corticotropin*

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
R.T.	26	M	1.1	....	2.0	4.4	1.1	....	3	3.3	300
E.K.	30	F	1.4	0.6	0.5	2.6	2.9	....	4	1.5	107
R.T.	40	F	2.2	1.9	2.9	3.7	....	....	3	1.5	68
G.N.	17	F	3.0	0.9	3.0	6.2	2.1	1.6	3	3.2	107
Average			1.9	1.1	2.1	4.2	2.0	1.6		2.4	146

TABLE 6.—*Record of Twenty-Four-Hour Urinary Corticosteroid Values of the Four Patients with Anterior Pituitary Insufficiency Showing Response to Intravenously Administered Corticotropin*

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
R.T.	26	M	(No cortin determinations made)								
E.K.	30	F	1.9	2.8	3.6	7.4	5.7	....	3	5.5	290
R.T.	40	F	2.3	3.1	8.1	9.4	....	....	3	7.1	308
G.N.*	17	F	10.6	11.1	10.5	18.2	3.9	3.1	3	7.6	72
Average			4.9	5.7	7.4	12.0	4.8	3.1		6.7	223

* Patient on 25 mg. cortisone daily.

TABLE 7.—*Record of Twenty-Four-Hour Urinary 17-Ketosteroid Values of Three Patients with Anterior Pituitary Insufficiency Showing Response to Intramuscularly Administered Corticotropin*

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
R.T.	26	M	0.6	2.2	1.9	3.1	1.3	1.5	3	2.5	417
A.L.	55	F	0.8	0.4	1.1	1.5	0	0.7	3	0.7	87
S.L.	50	F	1.5	6.2	10.3	16.0	5.8	8.1	3	14.5	968
Average			1.0	2.9	4.4	6.9	2.4	3.4		5.6	487

TABLE 8.—*Record of Twenty-Four-Hour Urinary Corticosteroid Values of the Three Patients with Anterior Pituitary Insufficiency Showing Response to Intramuscularly Administered Corticotropin*

Patient	Age	Sex	Control	Day					Day of Maximal Increase	Maximal Increase, Mg.	Maximal Increase, per Cent
				1st	2d	3d	4th	5th			
R.T.	26	M	1.4	6.4	5.0	3.4	2.0	....	1	5.0	357
A.L.	55	F	0.3	1.3	2.5	14.8	4.6	5.7	3	14.5	4,840
S.L.	50	F	0.4	3.5	0.4	16.5	3.3	9.1	3	16.1	4,030
Average			0.7	3.7	2.8	11.6	3.3	7.4		11.9	3,076

sufficient in many instances to provide evidence of adrenal cortical stimulation. However, by continuing the administration for three days and collecting urine, even on the days following, the reliability of the results was considerably increased.

A total of 13 tests was carried out on the six patients with anterior pituitary insufficiency (Tables 5-8). As with the control group, the most intense response was noted with the intramuscular repository injection and in most instances occurred on the third day. The data are presented graphically in Figure 2.

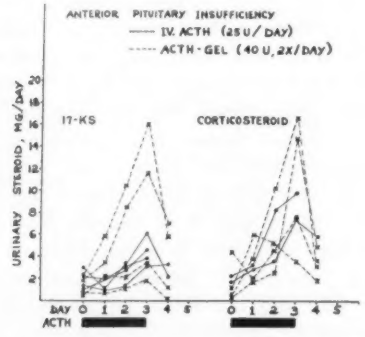

Fig. 2.—Individual data on patients with anterior pituitary insufficiency. The increments in urinary 17-ketosteroids and corticosteroids are given for both the intravenous and intramuscular methods of administration of corticotropin.

Nine tests were performed on five patients with known Addison's disease. These data are graphically shown in Figure 3 for comparison with the other results. The urinary steroids did not significantly change when corticotropin was administered.

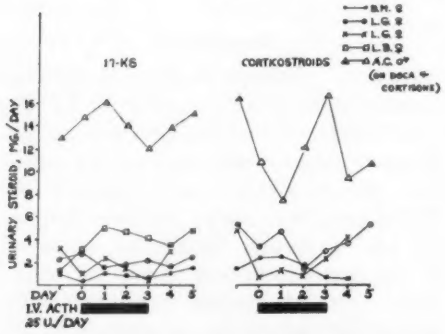

Fig. 3.—Individual data on patients with known adrenal cortical insufficiency. In these only the intravenous technique of administration of corticotropin was employed.

Comment

With the use of either intravenous or intramuscular corticotropin, conclusive evidence of stimulation of the adrenal cortex could be obtained in almost all cases by the methods described. With control values of steroid excretion greater than 2.0 mg. per 24 hours, increments greater than 100% in either 17-ketosteroid or corticosteroid excretion were considered an adequate response. When dealing with very low control levels (less than 2.0 mg.) only increments over 200% could be considered significant. By these criteria, only three of the patients in the control groups failed to respond adequately. Thus, if adrenal cortical insufficiency is still considered doubtful, the test should be repeated or corticotropin continued for more than three days. If the urinary 17-ketosteroid determinations alone are considered, the number of patients who failed to significantly increase the amount excreted is quite high. Using corticosteroids alone, a much smaller number failed to show adequate responses. However, when both determinations are used, only a small percentage of patients with intact adrenals failed to significantly increase the excretion of either 17-ketosteroid or corticosteroid. Thus, in performing a corticotropin test, the use of both determinations is most apt to give a definitive result, but the corticosteroids rise more consistently.

A comparison of results of the two methods of corticotropin administration in our hands reveals that a considerably greater response was observed with the use of the intramuscular repository injection preparation. With intravenously administered corticotropin there was an average maximal increase in 17-ketosteroid excretion of 160%, as compared with 252% by the intramuscular method. The average maximal increase in corticosteroid values by the intravenous method was 441%, by the intra-

muscular method, 607% (Tables 1-4). If the average daily increments (rather than maximal increments) are plotted, similar results are observed (Fig. 1). From these data it can be concluded that the repository corticotropin injection, used in the manner described, produced more pronounced and prolonged stimulation of the adrenals than did the corticotropin administered intravenously over a five- to six-hour period. It is probable that equal or greater stimulatory effect would have been obtained by the intravenous method if the period of infusion were prolonged to 8 or 10 hours or if it were given continuously over the entire three-day period. With the intramuscular administration of repository corticotropin injection at 12-hour intervals, a continuous release of corticotropin into the circulation was achieved without the disadvantage of indwelling needle and restricting infusion apparatus. The simplicity in administration is a factor of major importance in comparing techniques. In an occasional case, intramuscularly administered corticotropin may be rapidly inactivated at the site of injection and consequently fail to exert a stimulatory effect on the adrenals. Such cases are uncommon and have usually been associated with previous prolonged periods of corticotropin administration. In these cases an intravenous corticotropin test would establish a satisfactory response.

It is possible that the plasma steroids are more sensitive indicators of adrenal cortical response to corticotropin than are the urinary steroids; however, we have had no experience with this technique.

Further evidence of the superiority of the intramuscular repository injection as compared with the intravenous corticotropin, given over a five- to six-hour period, can be drawn from the data on the cases of anterior pituitary insufficiency (Tables 5 through 8). While the limited number of cases makes a precise evaluation impossible, a definite trend can be demonstrated in the results. When intravenous corticotropin was used, the response was slightly delayed and less intense when compared with the control groups. With the intramuscular repository injection, however, the response was prompt and of considerably greater magnitude than that observed in the control patients with chronic debilitating illnesses. The 17-ketosteroid values increased by an average of 177% by the intravenous method and 487% by the intramuscular method. The corresponding corticosteroid increases were 223% and 3076%. In one case the actual increment was obscured by cortin values which were elevated by the administration of cortisone.

In view of the great individual variations in response of the control group, it would not be possible by these techniques to differentiate a patient with anterior pituitary insufficiency from a sick patient with intact pituitary and adrenals who had initially low urinary steroid values. Since patients with pituitary insufficiency usually have adrenal atrophy of a mild or severe degree and are sensitive to stress, it is unlikely that the techniques employed here are adequate to detect "potential" adrenal insufficiency. Such differentiation might be possible with more precise quantitative procedures.

On the other hand, the cases of secondary adrenal insufficiency were readily distinguished from those of primary adrenal insufficiency. No significant effect on either 17-ketosteroid or corticosteroid excretion in these cases was demonstrated after administration of corticotropin by either route (Fig. 3).

Summary

Data are presented on 35 patients who received intravenous corticotropin (20-25 U.S.P. units for five to six hours) and on 22 other patients who received intramuscular repository corticotropin injection (40 clinical units twice daily) for three days to test adrenal cortical function as measured by increments in urinary steroid excretion. These were sick patients with intact pituitary and adrenal glands, and many had very low control levels of urinary steroid. By either method a significant rise (100% or greater if the control level was above 2.0

mg. and 200% or greater if the control value was very low, i.e., less than 2.0 mg.) in either the urinary 17-ketosteroids or the corticosteroids was observed in 54 of 57 patients studied. When an insignificant rise occurred in one urinary fraction, there usually was a significant rise in the other, the corticosteroids being the more sensitive indicator of adrenal activity. Occasionally, significant increments were observed by the first or second day of corticotropin administration, but most consistent results were observed if the corticotropin was administered for three days. Similar results were observed in several patients with anterior pituitary insufficiency, while no rise was observed in the cases of chronic adrenal cortical insufficiency.

The results obtained by the use of intramuscular repository corticotropin injection were more conclusive than those with intravenous corticotropin given over a five- to six-hour period. No doubt much longer or continuous periods of infusion of intravenous corticotropin would have given better results, but the technique is inconvenient. Thus, most consistent results can be expected if increments in corticosteroids are measured rather than the 17-ketosteroids, if the corticotropin is administered for at least three days, and if it is administered intramuscularly. It is apparent that the measurement of the increments in urinary steroids under the influence of corticotropin provides an accurate, safe, and direct test of gross adrenal cortical function. It is likely that tests of this nature will largely replace older tests for chronic adrenal cortical insufficiency, especially in patients with complicating illnesses.

In view of the considerable individual variations in steroid output, it was not possible clearly to differentiate patients with known anterior pituitary insufficiency from sick patients with intact adrenal and pituitary function. Therefore, it is not likely that these techniques are sufficiently quantitative to detect "potential" adrenal cortical insufficiency, such as might be present in a person who has been on exogenous hormone therapy.

Mrs. Marian Wisniewski performed the steroid assays.

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Adrenal Cortical Activity in Gastric Carcinoma

I. Studies of Plasma 17-Hydroxycorticosteroid Levels

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Adrenal cortical function in gastric cancer has been the subject of previous investigations. Dobriner and co-workers,[1] noting the presence of the abnormal steroid metabolite 11-oxyetiocholanolone on paper chromatography of urinary extracts in gastric cancer patients, postulated a disordered function of the adrenal cortex. This abnormal steroid metabolite was also present in patients with Cushing's disease.[2]

Young and co-workers,[3] studying glucose metabolism in patients with gastric carcinoma, observed that supplementary adrenal cortical extract was necessary to produce normal hepatic glycogen deposition in patients who were receiving oral glucose feedings.

Homburger and co-workers[4] have reported a disturbed water and electrolyte balance in gastric cancer patients, simulating in some respects that seen in adrenal hypofunction.

Rhoads[5] applied the Kepler and the Cutler-Power-Wilder tests to two patients with gastric cancer in order to investigate the connection, if any, between neoplasm of the stomach and adrenal hormonal imbalance. The results obtained were similar to those expected in patients with a hypofunctioning adrenal cortex.

The effect of intramuscularly administered corticotropin on the uric acid/creatinine ratio, phosphorus/creatinine ratio, potassium/creatinine ratio, and eosinophile levels, was reported by Reifenstein and co-workers.[6] The failure of response to corticotropin (ACTH) stimulation of the uric acid/creatinine ratio and the phosphorus/creatinine ratio was interpreted as supporting the concept of adrenal cortical dysfunction; although the eosinophile responses and the potassium/creatinine ratios were normal in these subjects.

Thus, the possibilities of both qualitative and quantitative dysfunction of the adrenal cortex have been raised in patients suffering from gastric carcinoma. This alleged dysfunction, if any, remains to be clearly defined.

Improved techniques for measuring the plasma free and conjugated 17-hydroxycorticosteroids are now available and offer tools with which to further evaluate the adrenal cortex.* It seemed pertinent to reevaluate adrenal cortical function in gastric carcinoma, utilizing these parameters together with concomitant studies of urinary 17-hydroxycorticoids and 17-ketosteroids.

Materials

Determination of plasma free and total 17-hydroxycorticosteroids were carried out in nine normal subjects (seven men and two women) rang-

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Fellow of the W. K. Kellogg Foundation and the American College of Physicians (Dr. Rozenbojm); This work was done during the tenure of a Postdoctorate Research Fellowship from the National Cancer Institute (Dr. Krakauer); Assistant Professor of Medicine, Harvard Medical School (Dr. Gray).

* References 8 and 9.

ing in age from 23 to 65 and in eight patients with gastric carcinoma (five men and three women) ranging in age from 58 to 79. The diagnosis was established by the usual x-ray or gastroscopic criteria, with confirmation obtained by laparotomy or by biopsy of metastatic site in each instance.

Following control determinations, 25 mg. of crystalline corticotropin (The Armour Laboratories was given intramuscularly to each subject, with subsequent collections of four- and six-hour blood samples.

Determinations of urinary 17-hydroxycorticoids and 17-ketosteroids were carried out in an unselected group of 18 patients with gastric cancer. Five of these patients were those studied with blood steroid levels. In addition, the urinary steroid determinations were carried out in a group of 50 normal male medical students. To evaluate the effect of larger doses of corticotropin on the urinary steroids, three patients with gastric carcinoma receiving doses of crystalline corticotropin varying from 50 to 100 mg. daily for one to four days were studied with urinary 17-hydroxycorticoid and 17-ketosteroid determinations.

Methods

A. Blood 17-Hydroxycorticosteroid Determinations

1. *Plasma Free 17-Hydroxycorticosteroid.*—The method utilized was a modification[7] of the procedure of Nelson and Samuels[8]. Heparinized plasma was obtained from 20 cc. of venous blood drawn between 8 and 9 a. m. in each patient. Similar samples were obtained four and six hours following the administration of 25 mg. of crystalline corticotropin (The Armour Laboratories) given intramuscularly. The term "free" 17-hydroxycorticosteroid, as used in this study, refers to adrenal cortical steroids with a 17, 21-dihydroxy, 20-ketone group (cortisone, hydrocortisone, and their hydrogenated derivatives). This method does not measure the conjugated forms of these steroids in plasma. All levels of free 17-hydroxycorticosteroids are expressed in micrograms per 100 ml. of plasma.

2. *Plasma Conjugated 17-Hydroxycorticosteroids.*—The conjugated serum 17-hydroxycorticosteroids were measured from the residue after the Nelson-Samuels chloroform extractions had been carried out. This method for determining the conjugated form of these plasma steroids was adapted from the method of Reddy and Thorn[9] and is based on the determination of the butanol-soluble 17,21-dihydro-20-ketosteroids. All results are given in micrograms per 100 ml. of plasma.

B. Urinary 17-Hydroxycorticosteroid Determinations

Twenty-four-hour urine collections (7 a. m. to 7 a. m.) were carried out on a control day and for the day of the corticotropin administration. A modification of the method of Reddy, Jenkins, and Thorn was used.[10]

C. Urinary 17-Ketosteroid Determinations

In each of the above urine samples the urinary 17-ketosteroids were determined by a modification of the method of Drekter and co-workers[11]

TABLE 1.—*Free and Total Plasma Hydroxycorticosteroid Levels in Normal and in Gastric Cancer Patients*

	Free 17-Hydroxycorticosteroids, γ/100 Cc.			Total 17-Hydroxycorticosteroids, γ/100 Cc.		
	Basal	4 Hr. After Corticotropin	6 Hr. After Corticotropin	Basal	4 Hr. After Corticotropin	6 Hr. After Corticotropin
			Normal (9)			
	12.7	28.2	12.7	37.4	72.5	63.5
	10.8	24.5	17.6	35.0	55.0	----
	11.9	20.2	12.7	58.0	101.7	69.7
	11.8	21.6	12.7	48.3	93.1	65.7
	12.8	28.2	23.1	44.3	82.2	95.1
	11.2	21.0	15.9	44.2	91.5	82.9
	11.6	----	12.8	49.9	----	83.5
	11.7	26.0	----	40.7	88.5	----
	10.5	24.0	----	39.5	66.5	----
Mean	11.7	24.3	15.4	44.1	81.4	76.9
			Gastric Cancer (8)			
	13.4	41.6	24.8	70.0	80.0	----
	9.4	20.0	16.0	13.8	----	----
	12.0	25.6	20.4	48.0	217.0	296.0
	15.0	35.5	22.6	72.8	86.0	----
	20.5	30.5	20.7	41.9	55.5	23.2
	17.5	41.6	----	62.0	113.0	----
	13.8	24.2	----	47.0	77.7	----
	11.3	27.6	----	29.1	68.6	----
Mean	14.1	30.8	20.9	48.1	99.7	----

TABLE 2.—*Effect of Corticotropin upon Free and Total Plasma 17-Hydroxycorticosteroid Levels*

	Mean Free 17-Hydroxycorticosteroids, γ/100 Cc.			Mean Total 17-Hydroxycorticosteroids γ/100 Cc.		
	Control	4 Hr. After Corticotropin	6 Hr. After Corticotropin	Control	4 Hr. After Corticotropin	6 Hr. After Corticotropin
Normals (9)	11.7 (S.E.±0.8)	24.3 (S.E.±3.3)	15.3 (S.E.±1.5)	44.1 (S.E.±2.4)	81.4 (S.E.±5.5)	76.9 (S.E.±5.1)
Gastric Cancer (8)	14.1 (S.E.±1.3)	30.8 (S.E.±2.8)	20.8 (S.E.±1.4)	48.1 (S.E.±7.1)	99.7 (S.E.±20.6)	.....

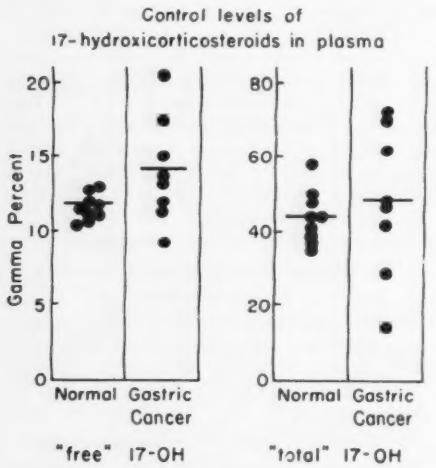


Figure 1

whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[19]

Results

I. Plasma 17-Hydroxycorticosteroids

A. Control Levels.—1. Normal Group: In nine normal subjects the mean plasma free 17-hydroxycorticosteroid level was 11.7γ per 100 cc. (S.E.±0.8). The mean plasma total 17-hydroxycorticosteroid level in this group was 44.1γ per 100 cc. (S.E.±2.4) (Tables 1 and 2, Fig. 1).

2. Gastric Cancer: In eight patients with gastric carcinoma the mean plasma free 17-hydroxycorticosteroids was 14.1γ per 100 cc. (S.E.±1.3). This mean value is not significantly greater than that for the normal group ($P>0.05$).

The mean plasma total 17-hydroxycorticosteroid level was 48.1γ per 100 cc. (S.E.±7.1) (Tables 1 and 2, Fig. 1). This mean value for the total 17-hydroxycorticosteroids is not significantly greater than that for the normal ($P>0.5$).

B. Effect of Corticotropin on Plasma 17-Hydroxycorticosteroids.—1. Normals: Four hours following 25 mg. of crystalline corticotropin intramuscularly, the mean plasma free 17-hydroxycorticosteroid level was 24.3γ per 100 cc. (S.E.±3.3). At six hours the level of average mean free 17-hydroxycorticosteroids was 15.3γ per 100 cc. (S.E.±1.5). The mean total 17-hydroxycorticosteroid level at four hours following corticotropin was 81.4γ per 100 cc. (S.E.±5.5), and at six hours was 76.9γ per 100 cc. (S.E.±5.1) (Tables 1 and 2, Fig. 2). The percentage increase in free 17-hydroxycorticosteroids was 108% and that for the total 17-hydroxycorticosteroids was 84% four hours after corticotropin stimulation (Fig. 3).

2. Gastric Cancer: The range of values and the mean increase in the free and total 17-hydroxycorticosteroids four and six hours following 25 mg. of corticotropin intramuscularly are shown in Tables 1 and 2 and Figure 2. The mean level of free 17-hydroxycorticosteroids was 30.8γ per 100 cc. (S.E.±2.8) at four hours, and at six hours was 20.0γ per 100 cc. (S.E.±1.4). The mean total 17-hydroxycorticosteroid level was 99.7γ per 100 cc. (S.E.±20.6) four hours after corticotropin. The total 17-hydroxycorticosteroid level at six hours was determined in only two subjects, with values as shown in Table 1. The percentage increase in the free 17-hydroxycorticosteroids was 118% and in the total 17-hydroxycorticosteroids was 107% four hours following corticotropin stimulation (Fig. 3). There was no significant difference in the

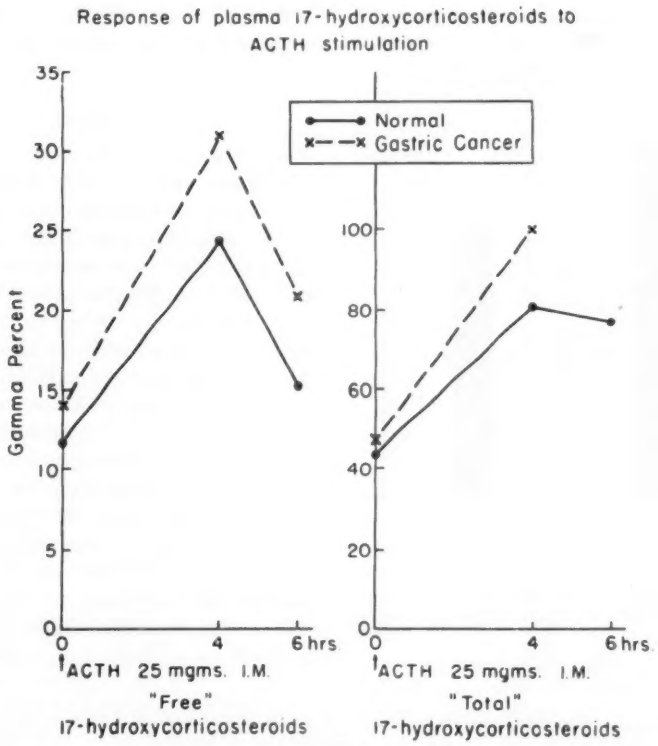


Figure 2

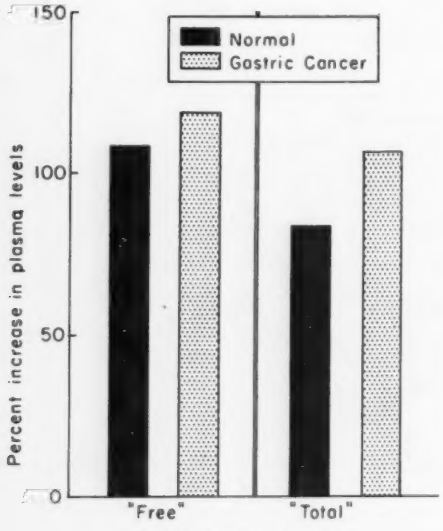
percentage increase in the plasma free or total 17-hydroxycorticosteroids comparing the gastric cancer with the normal group at the four-hour period ($P>0.5$).

II. Urinary Adrenal Steroid Control Levels

A. Control Levels.—1. Normal Group: The mean urinary 17-hydroxycorticoid level in 50 normal subjects was 5.8 mg./24 hours (S.E.±0.3). The mean level of the urinary 17-ketosteroids in these subjects was 14.4 mg/24 hours (S.E.±0.6) (Table 3).

2. Gastric Cancer: Urinary 17-hydroxycorticoids were determined in 18 patients with gastric cancer, with a mean value of 7.0 mg/24 hours (S.E.±0.9). The mean urinary 17-ketosteroid level in this group was 7.3 mg/24 hours (S.E.±0.8). Five patients in this group were studied with blood steroid determinations as well. The mean urinary 17-hydroxycorticoid levels in the cancer group did not differ significantly from the normal ($P>0.5$) (Table 3). No comparison was made between the cancer group and the normal in regard to the urinary 17-ketosteroids in the urine because of the disparity of age and sex, both of which are important factors in the ketosteroid levels.

B. Response of Urinary Adrenal Steroids to Corticotropin.—In five patients with gastric cancer to whom 25 mg. of corticotropin was given intramuscularly, no significant increase was noted in either the urinary 17-hydroxycorticoids or urinary 17-ketosteroids, comparing a 24-hour urine collected following the corticotropin with a control day. However, in three patients receiving larger doses of corticotropin (respectively, 50 mg. of repository corticotropin injection for one day, 100 mg. crystalline corticotropin for three days, 100 mg. crystalline corticotropin for four days) an



Plasma 17-OH corticosteroid levels four hours after ACTH stimulation in normal and gastric cancer groups

Figure 3

increased urinary steroid response to the corticotropin was noted, as shown in Table 4.

Comment

The studies of Young and co-workers,[3] Homburger and co-workers,[4] Rhoads,[5] and Reifenstein and co-workers [6] have suggested quantitative hypofunction of the adrenal cortex in patients with gastric cancer. However, most of the parameters utilized by these authors are indirect reflections of adrenal cortical activity. As Eik-Nes and coworkers have pointed out,[13] "most of these techniques rely on measurements of phenomena which are dependent on the effect of adrenocortical secretions on some special metabolic process, and do not involve the direct measurement of adrenocortical steroids. The frequent discrepancies between the clinical picture and these indirect tests indicate that they are not always reliable indices of adrenal function." The development of the methods for quantitative esti-

TABLE 3.—*Twenty-Four-Hour Urinary 17-Hydroxycorticoids and 17-Ketosteroids in Normals and in Gastric Cancer Patients*

	No. of Cases	Mean 17-Hydroxycorticoids, Mg./24 Hr.	Mean 17-Ketosteroids, Mg./24 Hr.
Normals	50	5.8 (S.E.±0.3)	14.4 (S.E.±0.6)
Gastric Cancer	18	7.0 (S.E.±0.8)	7.3 (S.E.±0.8)

TABLE 4.—*Response of Twenty-Four-Hour Urinary Steroids to Corticotropin in Gastric Cancer*

Corticotropin	17-Hydroxycorticoids, Mg./24 Hr.		17-Ketosteroids, Mg./24 Hr.	
	Control	After Corticotropin	Control	After Corticotropin
25 mg. I.M.	7.3	7.8	6.8	6.9
25 mg. I.M.	10.2	6.5	12.8	9.5
25 mg. I.M.	4.2	6.7	5.2	6.0
25 mg. I.M.	8.5	5.3	6.3	2.8
25 mg. I.M.	8.9	15.0	4.4	9.8
Mean	7.8	8.3	7.1	7.0
50 mg. repository injection I.M.	1.7	9.8	8.3	16.4
100 mg. I.M. (daily ×3)	9.2	70.2	7.3	17.1
100 mg. I.M. (daily ×4)	6.3	53.5	4.0	2.7

mation of adrenocortical function based on determination of 24-hour urinary steroid levels and more recently on determination of the blood 17-hydroxycorticosteroid levels has made it possible to measure adrenal cortical function and its response to corticotropin more directly.†

In our studies there was no significant mean difference in the free or total plasma 17-hydroxycorticoid levels or in the 24-hour urinary 17-hydroxycorticoid output, comparing the gastric cancer group with the normal. This would seem to indicate that in the basal state, the cancer group does not differ from normal in regard to quantitative adrenal cortical output. Further, the cancer group demonstrated the expected response to 25 mg. of intramuscularly administered corticotropin with elevation of the blood corticosteroid levels at the four- and six-hour periods similar to that seen in normal persons. The percentage increase following the corticotropin stimulus in gastric cancer did not differ significantly from the normal percentage increase.

In the limited number of patients studied with gastric cancer, no appreciable rise in 24-hour output of urinary 17-hydroxycorticoids or 17-ketosteroids could be detected following the stimulation with 25 mg. of crystalline corticotropin intramuscularly (Table 4). The lack of a urinary steroid response to this dosage of corticotropin has also been noted in normal persons.‡ A minor transient increase of urinary corticoid output following minimal stress or small doses of corticotropin stimulation of short duration may not be detected in the 24-hour urinary steroid output because of the factors of dilution and rebound inhibition, whereas they may be demonstrated by blood determinations. For this reason three patients with gastric cancer were given larger doses of corticotropin, after which the normally expected increase in urinary steroid output did occur, as indicated in Table 4.

† References 14 and 15.

‡ Renold, A. Personal communication to the authors.

In conclusion, this study would appear to indicate that no quantitative abnormality of adrenal cortical function is present in gastric cancer. No attempt was made herein to evaluate qualitative differences in steroid excretion. In this regard, the relationship of abnormal adrenal cortical activity and gastric carcinoma remains to be further investigated.

Summary

Plasma free and total 17-hydroxycorticosteroid determinations and concomitant urinary 17-hydroxycorticoid and 17-ketosteroid studies were carried out in patients with gastric cancer and in suitable control subjects.

No appreciable difference in the mean basal plasma steroid levels or in the 24-hour urinary steroid levels was evident in the cancer group compared with the normal.

Patients with gastric cancer presented a normal response to corticotropin administration.

It is concluded that there is no quantitative adrenal cortical dysfunction in patients with gastric carcinoma.

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A Clinical and Bacteriologic Evaluation of Novobiocin in Seventy-Five Patients

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Novobiocin, a newly developed antibiotic that is produced by a species of Streptomyces, was discovered almost simultaneously by two independent groups of investigators.* As reported by Frost and co-workers[3] and Wilkins and co-workers,[4] novobiocin was active in vivo and in vitro against Gram-positive cocci, Proteus, corynebacterium, Pasteurella, and Neisseria. No cross resistance has been found between novobiocin and other clinically useful antibiotics. Although the drug was obtained from two different sources, the common identity of the compound has been established by the infrared absorption spectrum and chemical and biologic methods.†

We have used novobiocin in the treatment of 75 patients with various diseases. This paper presents the results obtained.

Methods

Seventy-three patients were treated at the Research and Educational Hospitals, University of Illinois, and the Westside Veterans Administration Hospital and one case each at Hines Veterans Administration and the Cook County Hospital. We are indebted to the staffs of these hospitals for their cooperation in this study.

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From the Research and Educational Hospitals, University of Illinois, Westside Veterans Administration Hospital, and the Departments of Medicine, Preventive Medicine and Pediatrics, University of Illinois.

* References 1 and 2.

† References 5 and 6.

Of the 75 patients, 9 had either leukemia or polycythemia and were followed with leucocyte counts, platelet counts, and hematocrit readings to see if a drop in any of these indices would occur while novobiocin was being administered.‡ Appropriate pretreatment cultures § were obtained from all of the 66 patients with infections and from 45 of these patients during and after novobiocin therapy. Novobiocin ‖ was given orally, and unless otherwise stated, the daily dose was 30 mg. per kilogram of body weight in children, or 2 gm. in adults. One patient was given 500 mg. of intramuscular novobiocin for the first two doses of her course of therapy. The lowest and highest doses used orally per day were 1 gm. and 8 gm., respectively. Two patients were given 2 gm. of erythromycin daily and one patient 6 gm. of spiramycin ¶ daily along with novobiocin.

Serum concentrations of novobiocin were determined in serial twofold dilutions, by the use of Micrococcus pyogenes var. aureus, 209P,# as the test organism. The patients were observed daily for evidence of untoward reactions. Whenever possible, a subsequent test dose or course of novobiocin was given to patients manifesting reactions. Leucocyte counts and hemoglobin determinations were done on all patients at least twice a week while the drug was being used. Specimens of urine were examined at frequent intervals.

‡ Dr. John Louis cooperated in these studies.

§ Dr. Robert Hoffman and his staff in the clinical bacteriological laboratory of the Research and Educational Hospitals, University of Illinois, assisted in this study, and Margaret Mellody, Mary Rubenis, and Mae Hasegawa gave technical assistance.

‖ The novobiocin was supplied in the following forms: (1) Albamycin in capsule form as the acid sodium salt by The Upjohn Company; (2) Albamycin as the calcium salt in suspension by The Upjohn Company; (3) Cathomycin as the acid sodium salt in capsule form by Sharp & Dohme, Division of Merck & Co., Inc.; (4) Albamycin as the acid sodium salt for (intramuscular and intravenous) use by The Upjohn Company.

¶ Supplied by Sharp & Dohme, Division of Merck & Co., Inc.

Supplied by The Upjohn Company.

TABLE 1.—*Clinical Results of Treatment of Various Infections with Novobiocin*

Type of Infections	No. of Patients	Clinical Response	
		Good	Poor
A. Pneumococcal infections			
1. Pneumonia	9	7	2
2. Nonpneumonic respiratory infections	6	4	2
3. Pneumonia, presumably pneumococcal	11	11	0
B. Streptococcal infections	5	4	1
C. Staphylococcal infections			
1. Pneumonia	1	0	1
2. Meningitis	1	1	0
3. Bacterial endocarditis	1	1	0
4. Bacteremia	1	1	0
5. Multiple abscesses	2	0	2
6. Pyelonephritis	2	0	2
7. Fibrocystic disease (Staphylococcus predominating in sputum)	3	2	1
8. Wound abscess	2	2	0
9. Cellulitis	3	3	0
10. Osteomyelitis	2	2	0
11. Salpingitis	1	1	
D. Enterococcal infections			
1. Pyelonephritis	4	0	4
E. Proteus infections			
1. Pyelonephritis	1	0	1
2. Osteomyelitis	1	1	0
F. Miscellaneous infections			
1. Actinomycosis	1	0	1
2. Lung abscesses	2	0	2
3. Pneumonia, mixed infection	1	1	0
4. Acute upper respiratory infections	6	5	1

Results

Table 1 shows the clinical response of the patients with infections. The response was classified as good when subjective complaints and physical and laboratory findings rapidly improved after treatment. Poor results included those patients whose clinical condition did not improve or deteriorated.

Among 20 patients with proved or presumed pneumococcal pneumonias, poor results were observed in 2. One patient, a 32-year-old Negro man, had severe dyspnea, copious rusty sputum, and clinical signs and roentgenologic evidence of pneumonia of the left upper lobe. The leucocyte count was 2550 cells per cubic millimeter, and the pretreatment specimens of sputum contained pneumococci. Novobiocin therapy was started on the third day of the disease. After 24 hours, no improvement was evident. The leucocyte count was 2050 cells per cubic millimeter, and blood cultures taken at this time subsequently were demonstrated to contain pneumococci. Novobiocin was discontinued and penicillin administered in doses of 600,000 units per day. Defervescence occurred within 14 hours, and the patient's clinical condition improved correspondingly. Subsequent blood cultures showed no growth.

The second patient had a long history of asthma and recent evidences of cerebral arteriosclerosis. She was lethargic, disoriented, febrile, and dyspneic, with a productive cough. Roentgenograms showed patchy infiltration of the right lower lobe. Novobiocin was started on the fourth day of her illness and was given by gastric tube. On the second and third days of therapy, pneumococci still could be cultured from the sputum, and her clinical state remained unchanged. Penicillin was substituted for novobiocin after six days of therapy. This was followed by defervescence, clearing of her mental status, ability to take oral fluids, and general clinical improvement within three days.

Pneumococci were cultured from the sputum of one patient with acute bronchitis, from the throats of four patients with pharyngitis, and from the nose of one patient with sinusitis. The response to novobiocin therapy was poor in two patients in this group.

One patient had sinusitis with a positive culture of pneumococci from the nose. After 48 hours of therapy, the culture was still positive for pneumococci, but on the third day the pneumococci had been replaced by a novobiocin-sensitive stain of Staphylococcus. Because the patient felt no relief symptomatically, therapy was changed to penicillin at this time. The second patient with pharyngitis and otitis media was a 20-month-old girl. Pneumococci persisted in her throat in spite of therapy for seven days, and there was no clinical improvement.

Four of the five patients treated for a streptococcal pharyngitis showed a good clinical response, but, as may be seen in Table 2, streptococci still could be cultured from four patients on the 3rd, 6th, 9th, and

TABLE 2.—*Presence or Absence of Pathogenic Micro-Organisms in Follow-up Cultures after Novobiocin Therapy*

Organism	Source	No.	Became Neg.	Remained Pos.	Improved: Further Specimens for Culture not Obtainable
1. Diplococcus pneumoniae	Nose or Throat	5	4	1	0
	Blood	3	2	1	0
	Sputum	10	7	3	0
2. Streptococcus pyogenes	Throat	5	1	4	0
3. Micrococcus	CSF	1	1	0	0
pyogenes var. aureus	Urine	2	1	1	0
	Blood	3	3	0	0
	Sputum	6	1	4	1
	Throat	2	2	0	0
	Pus	11	3	3	5
4. Enterococcus	Urine	4	0	4	0
5. Proteus mirabilis	Urine	1	0	1	0
	Pus	1	0	1	0
6. Actinomycosis	Pus	1	0	1	0

12th days, respectively, after the beginning of therapy. A 5-year-old patient did poorly clinically and was the one from whose throat streptococci were cultured on the ninth day of therapy. The poor bacteriologic response in two of the other patients may have been due to inadequate therapy. Both of these patients were given only a 1 gm. daily dose, and one of them discontinued therapy after three days because she felt so well.

The patient with pneumonia caused by M. pyogenes var. aureus had an acute exacerbation of chronic leukemia from which he died four days after the beginning of novobiocin therapy. The patient with staphylococcal meningitis had a good clinical response to therapy with a combination of novobiocin and erythromycin, the dose of each being 2 gm. a day. Although bacterial cultures of the cerebrospinal fluid and blood still were positive on the sixth day of therapy, both subsequently became negative.

The 62-year-old Negro man with staphylococcal bacteremia had diabetes mellitus and a large abscess of the thigh which was incised and drained. Staphylococci were cultured from the pus. The abscess had increased in size while the patient received several other antibiotics in succession. Following a hip disarticulation, the blood culture became positive for M. pyogenes var. aureus. Novobiocin and spiramycin were administered concomitantly in doses of 2 gm. and 6 gm., per day, respectively. Further cultures of the blood were sterile. Many Gram-negative rods were cultured from the wound, but no staphylococci. The patient improved temporarily but later died. No abscesses or evidence of staphylococcal infection were found at autopsy. The surgical wound was not healed and formed a large ulcer. There was extreme inanition. No more specific cause of death was found.

Two children with multiple recurrent staphylococcal abscesses were treated with novobiocin for four months. One patient with leukemia received a dose varying from 20 mg. per kilogram of body weight the first two months to 40 mg. per kilogram of body weight the last two months. He developed chicken pox with a severe pyoderma due to the Staphylococcus and died. At autopsy multiple abscesses were present, all of which yielded cultures positive for M. pyogenes var. aureus. The other patient was a 6-year-old boy, who had had recurrent visceral staphylococcal abscesses since the age of one year. He received 40 mg. per kilogram

of body weight for four months. On this therapy fever continued and new abscesses appeared. In both patients, the coagulase-positive staphylococci of specific phage type cultured from the abscesses showed progressively increasing resistance to novobiocin during the first one or two months of therapy.

Three children with fibrocystic disease of the lung and recurrent pulmonary infections in which staphylococci predominated were given novobiocin for periods varying from three to seven months, the daily dose being approximately 30 mg. per kilogram of body weight. All three improved symptomatically soon after novobiocin therapy was started; their appetites increased, and they gained weight. Two of them maintained this improved status, and the staphylococci obtained from their throats showed no increase in resistance to novobiocin. The third patient died in acute right ventricular failure; the coagulase-positive Staphylococcus cultured from this patient showed increasing resistance to novobiocin during the three months of therapy.

The patient with salpingitis, caused by M. pyogenes var. aureus, had a profuse cervical discharge which cleared with 10 days of therapy with novobiocin. Culture from the cervix at the end of this period no longer showed staphylococci.

Neither of the two patients with pyelonephritis due to Staphylococcus responded satisfactorily to novobiocin therapy. Pyuria persisted, and symptoms remained unabated. The staphylococci disappeared from the urine temporarily, but were cultured again from the urine of one patient two weeks after therapy was discontinued.

One patient with disseminated lupus erythematosis and pyelonephritis caused by Proteus mirabilis (which was cultured from the urine and from tissue obtained on renal biopsy) was treated for eight days with novobiocin. The patient continued during that time to show marked costovertebral angle tenderness, fever, and pyuria, and the urine culture remained positive. The organism was not inhibited in vitro by 250γ of novobiocin.

A very obese 54-year-old white woman had dyspnea, copious yellow sputum, roentgenologic evidence of a right middle-lobe pneumonia, and a positive sputum culture for pneumococci. She was treated with tetracycline for approximately 12 days. During the week following discontinuance of this therapy, the patient's condition deteriorated; the pneumonia spread to the left lower lobe, and sputum cultures showed a mixed infection, with a predominance of M. pyogenes var. aureus. Because of the severity of her clinical condition and predominance of staphylococci on sputum cultures, the patient received two 500 mg. doses of novobiocin intramuscularly. These were followed by marked clinical improvement. Novobiocin therapy was then continued in doses of 2 gm. a day orally. Therapy was discontinued after one week when a generalized skin eruption appeared. Staphylococci were persistently cultured from the sputum, although less numerous than before. The patient finally developed multiple lung abscesses and empyema, which were drained surgically.

Table 2 shows the bacteria obtained before and after treatment with novobiocin arranged according to the source of the culture. Among 18 patients from whom Diplococcus pneumoniae was cultured before therapy with novobiocin, the cultures were negative in 13 after therapy. Among the five patients with persistently positive cultures, three had pneumonia (including the two who have been mentioned previously as failing to respond to novobiocin therapy). The third patient had a good clinical response, although pneumococci still were cultured from the sputum after five days of novobiocin therapy.

As stated previously, four patients had positive throat cultures for streptococci after treatment. The dose may have been inadequate in two of these patients.

In 7 among 24 patients from whom M. pyogenes var. aureus was obtained, the

organism persisted in appropriate cultures. As stated, in three of these a specific strain as determined by phage types became one-hundred-twenty-eight- to at least two-hundred-fifty-six-fold more resistant. Among the staphylococcal infections, the three of the four patients whose sputum cultures were persistently positive had fibrocystic disease of the lung. Organisms resistant to novobiocin appeared in only one. Of the three patients who had positive cultures from pus, two children had recurrent multiple abscesses. Strains that were resistant to novobiocin appeared in both patients.

The treatment of enterococcic urinary tract infections with novobiocin was unsuccessful both from the clinical and the bacteriologic standpoint, as also was novobiocin therapy in a patient with actinomycosis.

Untoward Reactions

Among the 75 patients treated with novobiocin, 14, or 18.7%, developed untoward reactions, as shown in Table 3. Two, or twenty-two per cent, of the nine patients with leukemia and polycythemia who received large doses of novobiocin developed untoward reactions. Leucopenia appeared in 2 patients during therapy, and a skin eruption in 12. The skin eruption was accompanied by hematuria which lasted for two days in one patient, by arthralgia in another, and by fever in two others. Eosinophilia occurred in five patients, four of whom had other untoward reactions. One patient developed a 14% eosinophilia on the sixth day of therapy with novobiocin without toxic manifestations. Two of the remaining four patients had eosinophilia associated with leucopenia and two had eosinophilia with a skin eruption. The eruptions were urticarial, maculopapular, or morbilliform and were usually accompanied by itching. All untoward manifestations appeared between the 6th and 27th days of therapy with novobiocin.

Patient 1 developed a leucocyte count of 2750 cells per cubic millimeter on the 13th day of therapy. Bone marrow showed

TABLE 3.—*Untoward Reactions Accompanying Novobiocin Therapy*

Patient	Reaction	Drug*	First Course Dose, Gm./Day	Day Reaction Began	Subsequent Course	
					Drug	Reaction
1	Leucopenia	A	1.5	13	A	Leucopenia
2	Leucopenia	A	2.0	17	†	
3	Morbilliform eruption	A	30 mg./kg.	6	--	
4	Morbilliform eruption	C	2.0	11	S A C S	Morbilliform eruption No reaction No reaction Morbilliform eruption
5	Morbilliform eruption	C	2.0	8	A	No reaction
6	Morbilliform eruption	A	4.0	21	C	Maculopapular eruption
7	Maculopapular eruption	A	2.0	10	A C	Pruritus No reaction
8	Maculopapular eruption	A	2.0	7	--	
9	Maculopapular eruption	A	1.2	8	--	
10	Maculopapular eruption	A	2.0	7	--	
11	Maculopapular eruption	A	2.0	12	--	
12	Urticarial and maculopapular eruption	A	2.0	9	A	No reaction
13	Urticaria	A	4.0	27	A	Urticaria
14	Morbilliform plus maculopapular eruption	A	2.0	9	A C	Fever & chills Fever

* A indicates Albamycin; C, Cathomycin; S, sulfisoxazole.
† Not given. First course continued for 14 days after onset of leucopenia. Leucocyte count rose to 5900 per cubic millimeter during this time.

granulocytic suppression with increased erythropoesis at this time. Two days later, after discontinuance of drug, the leucocyte count had returned to 5750 cells per cubic millimeter. Eight days later patient was given a test course of 500 mg. at eight-hour intervals for three doses. This was followed by fever and a fall in the leucocyte count to 3600 cells per cubic millimeter.

After Patient 2 developed leucopenia, his first course was inadvertently continued for 14 days. Despite this, the leucocyte count rose from 3500 to 5900 cells per cubic millimeter during this period.

Cathomycin was used as the initial drug for therapy for Patient 4. On the 11th day a severe morbilliform rash appeared and therapy was stopped. Four days later, sulfisoxazole therapy was begun on account of urinary-tract infection. On the sixth day of therapy with this drug, fever, edema, and an extensive morbilliform eruption appeared. Four days later, after subsidence of the rash, the patient was given a course of 2 gm. a day of Albamycin for five days, followed by a course of Cathomycin four days, without the occurrence of a reaction. When the patient was retested with a 500 mg. dose of sulfisoxazole, however, he again developed an extensive morbilliform eruption.

Patient 6 was a patient with leukemia who developed a morbilliform eruption and icterus on the 21st day of therapy on a 4 gm. daily dose of Albamycin. The leucocyte count was 4300 cells per cubic millimeter; the patient had received no antileukemic drugs for one month prior to the development of this count. At this time, her total bilirubin was 2.8 mg. per 100 ml., and the alkaline phosphatase, 1.1 units. The serum concentration of novobiocin taken three hours after her last dose was 1024γ per milliliter. The icterus subsided and the bilirubin returned to normal limits three days after discontinuance of the drug. The leucocyte count returned to 7200 cells per cubic millimeter in the same period of time. Eleven days after discontinuance of the drug, the patient was tested with a 500 mg. dose of Cathomycin and developed a localized maculopapular rash over both arms.

Increase in Resistance of Staphylococci to Novobiocin

Table 4 shows the resistance of strains of staphylococci obtained from four patients during novobiocin therapy. With the aid of bacteriophage typing, we have been able to demonstrate that in each of these cases the original strain of Staphylococcus has shown increasing resistance or has been replaced by a strain of greater resistance.

Patient B was a 2-year-old boy with leukemia and multiple staphylococcic abscesses. Staphylococci cultured from his lesions showed an eightfold increase in resistance to novobiocin during the first month of therapy. Subsequently, new strains of staphylococci that were resistant to novobiocin were recovered, but the primary strain which was also recovered at intervals appeared to increase in resistance. As previously related, he died after four months with generalized staphylococcic infection following the development of chicken pox.

Patient A was a 5-year-old girl who had fibrocystic disease of the lung and from whose sputum predominantly coagulase-positive staphylococci could be cultured. The original strain showed an eightfold increase in resistance to novobiocin after three weeks of therapy. During the next two months, this was replaced by strains that were much more resistant to staphylococci.

Patient C was a 6-year-old boy who had had recurrent multiple abscesses since the age of one year. He had received many antibiotics in the past. From May 9 to June 8, 1955, he received Cathomycin in doses of 30 mg. per kilogram of body weight. On Sept. 7 he was started on novobiocin in doses of 20 mg. per kilogram of body weight per day. The dose was increased on Oct. 10 to 40 mg. per kilogram of body weight. The staphylococci cultured at this time were moderately resistant to novobiocin. The patient continued to develop new abscesses and continued to receive

TABLE 4.—*Appearance of Resistant Strains of Micrococcus Pyogenes Var. Aureus in Four Patients Treated with Novobiocin*

Patient	Diagnosis	Date	Culture from	Phage Type					Minimal Inhibitory Concentration, γ/Ml.
				Group I	Group II	Group III	Group IV	Group M	
A	Fibrocystic disease of the lung	4/ 7/55	Sputum			7/53			0.98
		9/12/55*	Throat				42D		0.39
		9/16/55	Throat				42D		0.39
		9/23/55	Sputum			7/(53)/77†			0.195
		10/ 7/55	Sputum			(7)/42E	42D		6.25
		10/28/55	Sputum			0			12.5
		11/ 4/55	Sputum				42D		12.5
		11/13/55	Sputum			7/53/77			>25.0
		12/28/55	Sputum			(77)	42D	971	12.5
B	Recurrent multiple staphylococcal abscesses	9/15/55*	Abscess, neck			7/(53)/77			0.195
		10/ 1/55	Abscess, neck			7/77/(53)			0.098
		10/ 7/55	Abscess, abdominal wall			7/53/77			1.56
		10/ 7/55	Ear	79	(3A)/(3C)/(51)/(523)				
		10/12/55	Abscess, neck		51/523	6/7/42E/53/77			12.5
						6/7/42E/53/77/42B, 47C			6.25
		12/21/55	Abscess, head			(7)/(47)/53/(70)/77		971	12.5
		12/21/55	Abscess, leg			(7)/(47)/53/(70)/77		(971)	6.25
C	Recurrent multiple staphylococcal abscesses	1/25/55	Liver abscess			7/53/77			0.098
		2/ 7/55	Abscess, neck	79	(3C)	7/53/77			0.098
		4/ 8/55	Drainage wound	(79)		7/53/77			0.195
		4/21/55	Drainage wound	(79)		7/53/77			0.098
		5/ 6/55‡	Drainage wound	79		7/53/77			0.195
		8/30/55	Abscess, neck			7/53			12.5
		9/ 6/55*	Throat			7/53			12.5
		9/ 8/55	Abscess, neck	79		7/53			12.5
		9/13/55	Abscess, neck			7/53/77			12.5
		10/ 3/55	Abscess, neck			7/53/77			>25.0
		10/ 3/55	Abscess, abdominal wall			7/53/77			12.5
		10/ 8/55	Abscess, neck	79	(3A)/(3C)/(51)/(523)				
		10/17/55	Abscess, neck		(51)/(523)	(6)/7/(47)/53/77			12.5
		11/10/55	Abscess, neck			(6)/7/53/77			6.25
		11/15/55	Abscess, neck	(20)		7/53/77			12.5
						7/53/77			12.5
D	Fibrocystic disease of the lung	11/28/55*	Sputum			6/7/42E/53/54/77			
						42B, 47C		971	0.195
		12/13/55	Sputum			(6)/7/42E/47/53/54/70/77		971	0.78
		1/10/56	Sputum			53		971	12.5
		4/27/56	Sputum			47/73			12.5

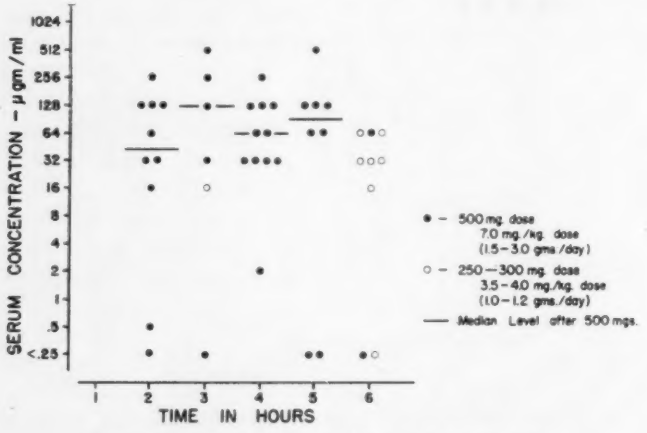
* Novobiocin therapy begun.
† Parentheses indicate a weak reaction, i.e., less than 50 plaques.
‡ Novobiocin given for the next four weeks.

novobiocin for six more months without any further increase in resistance to novobiocin.

Serum Concentrations

The serum concentrations of novobiocin in 44 specimens obtained from 12 adult patients at varying times after the administration of an oral dose of 250 mg. to 500 mg. of novobiocin are presented in the Figure. Between two and six hours after 500 mg. was given orally, the median level was 32γ to 128γ per milliliter. The maximum level during treatment with 500 mg. every six hours was 512γ per milliliter. In one patient who received 1.0 gm. of novobiocin every six hours by mouth, a serum concentration of 1024γ per milliliter was observed three hours after a dose on the 21st day of treatment. Where observations were made, however, the serum concentration after the first dose was nearly the same as was observed after several days of treatment. Thus, there was usually no cumulative effect. In some patients no antibiotic activity was found in the serum, and this finding will be discussed. Occasionally the presence and at another time the absence of antibiotic was observed in the serum of the same patient after an identical dose on different days. When treatment was discontinued an antibiotic level was demonstrable in the serum of most of the patients who were tested 8 hours after the last dose, and in one patient 13 hours later.

Among a small number of children from whom blood was obtained, the serum concentration of novobiocin after a 100 to 200 mg. dose (20-40 mg. per kilogram of body weight per day) was comparable to that shown for adults.



Serum concentrations of novobiocin in adult patients.

Comment

The development of each new antimicrobial agent offers a fresh opportunity for control of one or another of the remaining problems in the treatment of infections. Prominent among these problems are the control of infections associated with chronic diseases and the control of infections that are caused by strains of M. pyogenes var. aureus (staphylococci) that have become resistant to the previously used antibiotics. In addition, it is necessary that each new antibiotic be evaluated also as to its clinical effectiveness in common infections for which a suitable treatment is known, as well as in recalcitrant infections for which we are seeking a new and better treatment. Among the pharmacologic characteristics to be investigated are the relationship of dose to serum concentration, the relationship of concentrations obtained in body fluids to

in vitro antibacterial activity, and, finally, the toxic and symptomatic effects produced among humans.

Prior to clinical trial novobiocin showed great promise because it was found to inhibit effectively in vitro most strains of Staphylococcus at concentrations of the drug that were only a fraction of the level that could be obtained in the serum following the oral administration of a nontoxic dose. Thus, it seemed possible theoretically that the emergence of resistant strains from first-step mutants might be suppressed, and if this were a small and obligatory step in the development of resistance such strains might not occur at all. Furthermore, cross resistance of strains to other common antibiotics and novobiocin appeared to be negligible. Although this aspect of the drug appeared to offer the greatest promise, the antibacterial spectrum of novobiocin also included micro-organisms from other genera.

The clinical and bacteriologic response of patients with staphylococcal infections who have been treated with novobiocin corroborates the laboratory evidence for the effectiveness of the agent in suppressing the growth of staphylococci. It was disappointing, however, that in six patients the clinical response was poor and that staphylococci persisted in 8 of 25 specimens that were cultured for bacteria near the conclusion of treatment. The development by the strain of resistance to novobiocin, the persistence in the lesion of a sensitive strain, and the implantation of a new strain during treatment all were observed among the bacteriologic failures. Thus, the mechanisms that with increasing frequency have accounted for failure in the treatment of staphylococcic infections with previous antibiotics were observed among the patients treated with this antibiotic, and it must be anticipated that they likewise will be encountered with increasing frequency if there is widespread use of novobiocin. Since the development of resistance to novobiocin by some strains of Staphylococcus is well documented in these studies, it is recommended that another antibiotic that may suppress the emergence of such strains be used concomitantly when the treatment is expected to be prolonged. Studies on the effectiveness of such a combination are in progress. Because resistant strains appear to emerge from a group of seemingly facile organisms that successively have become resistant to several antibiotics, the actual value of treatment with a combination of any two antibiotics is problematical. The short courses of therapy needed for most infections probably would not cause a significant increase in resistance, but the secondary implantation of resistant strains may occur.

Novobiocin frequently failed to eradicate offending organisms from infections caused by other Gram-positive cocci: D. pneumoniae, S. pyogenes, and enterococcus.

Certain pharmacologic factors influencing the activity of novobiocin have become apparent in these investigations. The height of the serum concentration that is obtained following the administration of a standard dose is quite variable, with two general populations. In the majority of persons a significant concentration of antibiotic was demonstrable in the serum for six hours. Another group of persons, however, did not have an appreciable serum concentration when the serum was examined by microbiological assay for drug activity. The differences undoubtedly are exaggerated owing to the binding of novobiocin by serum proteins, which has been demonstrated by several workers.* In this respect the large differences in serum concentration might be an artefact relative to the conditions of in vivo infection. It is likely, however, that the degree to which novobiocin is absorbed from the gastrointestinal tract varies considerably, and one cannot be confident, therefore, of the effectiveness of any particular dose of novobiocin in all patients. If such is the case, routine examination of the blood for drug activity must be a part of the treatment regimen, especially when

* References 7 and 12.

the response of the patient is less than expected. Alternatively, one may depend on parenteral administration of novobiocin during the acute stage of the illness.

Depression of the activity of novobiocin per unit of drug in the body fluids as a consequence of protein binding cannot be evaluated yet for its importance in the treatment of patients. The implantation during treatment of some new strains of bacteria that were sensitive to novobiocin in vitro might indicate that inactivation by protein binding also is operative in vivo. On the other hand, the slight acidity of inflammatory exudates or the greater acidity of urine might favor novobiocin, which is more inhibitory in vitro at a pH of 4 to 7. Certainly the bond between novobiocin and serum protein is a loose one and does not destroy the antibacterial activity of the drug after disassociation.

The frequency of drug reactions among our patients was great and potentially serious. When treatment was omitted in these patients, the skin rashes disappeared without serious sequellae, lasting at the most four days. Prior to this report only a few patients have received a second course to elucidate the frequency and nature of subsequent reactions. Among eight patients who developed a skin eruption related to the administration of novobiocin and reported here, five had a recurrence within 24 hours after the drug was readministered. Among other patients in this study in whom the administration of a second course of novobiocin was delayed two weeks or longer after the previous omission of the drug, no recurrence of the initial reaction was observed during a brief course of retreatment. Whether the mechanism of the rash is an idiosyncracy, hypersensitization, or a toxic manifestation is not clear.

It is remarkable that one of the patients who developed a leucopenia during the treatment recovered a normal leucocyte count even though the administration of novobiocin was inadvertently continued. Despite this apparent reversibility, leucopenia should be considered a contraindication to continued administration of novobiocin until physiologic aspects of the leucocyte depression associated with the drug are better known. Leucopenia and eosinophilia, both of which have been noted by other investigators † were observed concomitantly in two patients. Eosinophilia was observed also in two patients with skin eruption and another without a rash. An increased total bilirubin also has been reported previously,[8] but since novobiocin or some metabolite of novobiocin produces a yellow pigment in the plasma,[8] one cannot be sure that this is a manifestation of liver insufficiency or hemolytic anemia. A concomitant assay of the serum level for novobiocin in one patient indicated a concentration of 1024γ per milliliter.

Summary

Seventy-five patients were given novobiocin by mouth.

The response to infections with Micrococcus pyogenes var. aureus was generally good except in cases where chronic tissue changes predisposed to continued infection.

Improvement was noted in patients with pneumococcic and β-streptococcic infections, but the response was often not as prompt and the eradication of the organism not as consistent as in cases where penicillin is used. No improvement was observed after administration of novobiocin to patients with infections caused by enterococcus or Proteus or in patients with actinomycosis or lung abscesses.

The median serum concentration of novobiocin after a standard dose was 64γ to 128γ per milliliter, but there was wide variation.

Untoward reactions were observed in 14, or 18.7% of the patients. Skin eruptions occurred in 12, eosinophilia in 5, leucopenia in 2, and jaundice in 1. Among eight of these patients who were given a second course of novobiocin, toxic signs or symptoms reappeared in five. Reactions to both Albamycin and Cathomycin were observed in two of the four patients to whom both preparations were given.

† References 8, 9, and 11.

Strains of staphylococci that were resistant to novobiocin appeared in four patients who were treated for three months or longer.

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Ophthalmoplegia, Steatorrhea, Phlebectasia, and Vascular Lipomas

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When one encounters an unfamiliar combination of signs and symptoms in a patient he must decide whether this is a coincidental assemblage collected by chance in one person or whether it deserves to be called a syndrome. This is not just a matter of musty academic interest for imaginative speculation. Insight into the processes of disease may come from intense scrutiny of the rare as well as the multiplication of large collections of the commonplace. Uniform groups of signs and symptoms which we encounter with some regularity may arise in two general ways. A genetic or metabolic error may produce a number of different lesions when several different organs or systems are involved. Or a disorder in one system or one organ affects others in turn and disorganizes function or distorts tissues removed in locus and differing in function from those at the site of the primary disorder.

At times a perceptive case report, or a survey of reported cases, of a rare disease will evoke an epidemic wave of new case reports; and no doubt a larger wave of examples recognized but not recorded. New insights may occur when there is intense or widespread interest. Reporting a case where chance has thrown together in one person a cluster of unrelated troubles will soon be forgotten. If it leads to the recognition of other similar examples, knowledge may accumulate and ultimately understanding may come. With such motives in mind, a patient with a peculiar combination of lesions is reported herewith.

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Report of Case

The patient was a 51-year-old man who worked as a clerk. He was first admitted to the Medical Service of the University Hospitals on July 9, 1951. His story was that for the previous 20 years he had experienced many fluctuations in a chronic illness characterized by abdominal distention with gas, loose, foul, "putty-like" stools, and weakness. He had had many programs of therapy outlined by various physicians and clinics, in the main consisting of special attention to diet with different combinations of liver extract, B-complex vitamins, particularly thiamine, and later vitamin B_{12}, and a regimen of rest. Though there had been remissions and exacerbations, it was his impression that they were entirely unrelated to therapy. They did not begin soon after therapy was started or was changed. They might happen at any time with or without treatment. A year before admission he began to note a drooping of his left eyelid, and at the same time he had increasing difficulty in focusing his eyes. Diplopia on lateral gaze then occurred. His hands and feet often felt cold and numb. At the time of admission he was having not more than two or three loose stools a day and his appetite was good. His main complaint was an overwhelming and progressive weakness which was now worse than ever. He was so unsteady on his feet that he was unable to walk. The abnormalities found in the physical examination included emaciation and pallor. The right pupil was slightly smaller than the left, but both reacted to light. Convergence was impossible, and there was extreme drooping of both lids. With his most vigorous effort, he could not raise his eyelids enough to look straight ahead but had to tilt his head back (Fig. 1). His tongue was smooth but not abnormal in color. Some papillae persisted. Very prominent veins coursed over the abdomen, chest, back, and extremities. Scattered at various points beneath this network of veins were lesions that felt like lipomas or fibromas—discs and button-like elevated vascular areas connected with large overlying veins (Figs. 2, 3, 4,

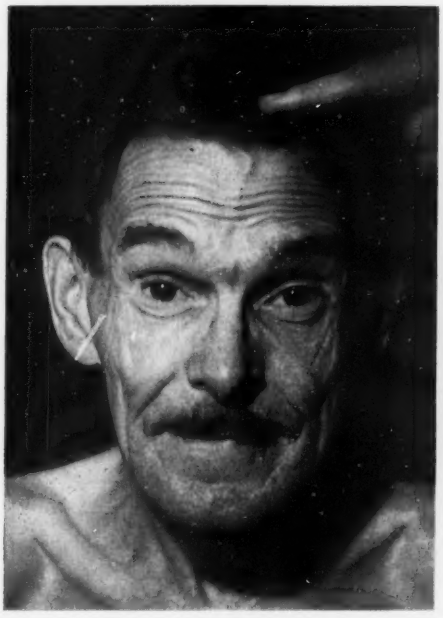

Fig. 1.—Maximal possible upward glance.

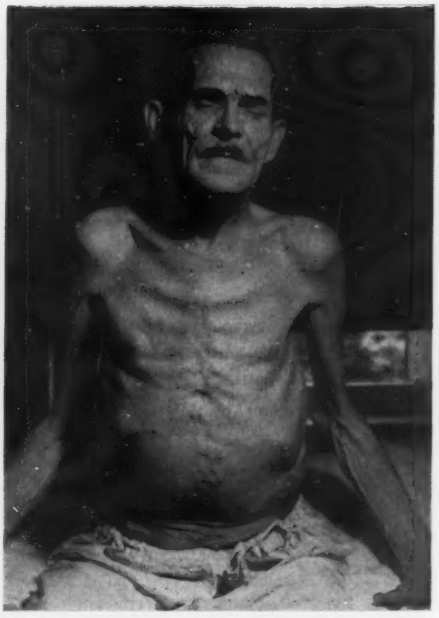

Fig. 2.—Black-and-white photograph of the patient, showing prominent veins and the lumps underlying them.

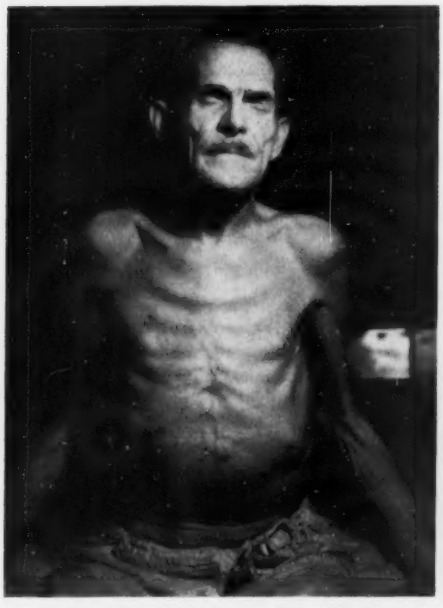

Fig. 3.—Infrared photograph in the same position as in Figure 2. Gynecomastia is noted, and the relation of the vascular lipomas to the large veins can be seen.

Fig. 4.—Black-and-white photograph of the anterolateral aspect of the lower abdomen on the left, showing large veins and numerous subcutaneous lumps.

Fig. 5.—Infrared photograph of the same area as in Figure 4, taken from a different angle. The intimate connection of the overlying veins and vascular lipomas is demonstrated.

and 5). Sustained pressure on these discs for a period of several minutes would flatten them, but some of the tissue could not be compressed and remained palpable. The pattern of veins was not that of the commoner networks seen in obstruction of superior vena cava, inferior vena cava, or in hepatic cirrhosis or in the superficial portal anastomotic veins of the Cruveilhier-Baumgarten syndrome. The patient had bilateral gynecomastia. The liver was not palpable. There were small axillary nodes. The muscles generally were much wasted, but there was no tenderness and no fibrillation. He was unable to raise his legs when he was in the supine position. No tendon reflexes remained. There was no serious difficulty in swallowing. Although weakness was extreme, no movements were completely absent. There was some decrease in vibratory sense in the hands and complete loss in the legs. He had severe ataxia and complained of vertigo. Libido and potency were reduced.

Laboratory studies revealed hemoglobin of 8 gm. per 100 ml., red cell count of 3,250,000 per cubic millimeter, white cell count of 13,000, with 52% segmented polymorphonuclear leucocytes, 2% eosinophiles, 42% lymphocytes, and 4% monocytes. The hematocrit was 31%. The stool was clay-colored and fatty. Gastric juice contained free hydrochloric acid without histamine. Lumbar puncture was negative. The dynamics were normal, the pressure was 90 mm. of Hg. The Queckenstedt test was normal. There were no cells, the fluid was clear, and the gold curve was normal. The spinal fluid protein was 42 mg., chloride, 750 mg., sugar, 52 mg., per 100 ml. Study of the alimentary canal revealed a completely normal esophagus without web formation or varix and a normal stomach and duodenum. The "deficiency pattern" of the small bowel was observed. X-ray of the skull showed it to be somewhat demineralized, although the bony texture itself was normal. X-ray of the chest revealed increase in the markings throughout but especially in the second interspace on the left. The density appeared to be fibrotic in character. The bony marrow was normal; the blood urea nitrogen was 20 mg. per 100 ml.; calcium, 9.8 mg.; phosphorous, 2.5 mg.; alkaline phosphatase, 9.2 Bodansky units. A study of the stool revealed that the total solids were 10% of the total weight. Fats constituted 50% of the total solids. This is in comparison with our normal results of 25% of the total weight being solids and 25% of the solids being fat. There was only a trace of urobilinogen in the stool. The van den Bergh was less than 0.75 mg. The cephalin flocculation was 1+ and 2+ in 24 and 48 hours; fasting blood sugar, 68 mg. per 100 ml.; sulfobromophthalein (Bromsulphalein) (5 mg/kg. at 45 minutes) showed 6% retention.

It was the concensus of members of the medical and neurological staffs that this patient had Wernicke's syndrome as well as posterior column degeneration of the cord. Myasthenia gravis was excluded by appropriate tests.

On July 16, 1951, he was transferred to the metabolic ward for vitamin and nitrogen balance studies. The usual stool and urine collections were made. He was started on a low B-vitamin diet which supplied no more than one-third of the usual intake of all of the B-vitamins, but with 3 gm. of pantothenic acid and 1.5 gm. of pyridoxine added daily. He got 900γ of B_{12} intramuscularly on three successive days. There was no reticulocyte response. He was given large doses of thiamine parenterally, but no change in his condition was noted. He refused to take folic acid because it had caused considerable abdominal discomfort previously. Each day for three weeks he was given 300 mg. of pantoyltaurine, a pantothenic acid antagonist, without any noticeable change. He was given iron by mouth, although it was doubted that it would be absorbed well from his damaged small bowel. He was given four 250 cc. blood transfusions. Finally his hemoglobin came up to 11 gm. We tried various diets, but he did not improve. He did better when choosing his own food, using his judgment based on long experience in varying his diet. For short periods his diarrhea

and abdominal discomfort would decrease, and then recur for no apparent reason.

Comment

Biopsy of the partially compressible tumors connected with the veins revealed them to be vascular lipomas (Fig. 6). These mesodermal tumors had their vascular components well demarcated. Although the vascular element predominated, the presence of much adipose tissue led to its classification among the vascular lipomas. The major element was certainly angiomatous with only a relatively small amount of lipomatous tissue. There has been a good deal of speculation about such lesions, and even at the time of original study there was some difference of opinion as to what it was.

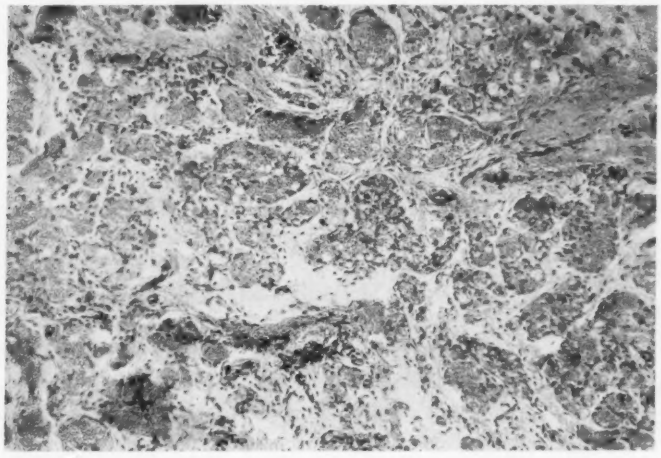

Fig. 6. — Microscopic section of one of the subcutaneous lesions, revealing numerous intercommunicating vascular spaces containing red cells and areas of increased fat.

The pattern of veins over the abdomen is that of a general reticular network of large veins. It was not the kind of pattern found with obstruction of either vena cava. In some instances it is difficult to decide whether prominent veins over the abdomen merely appear larger than normal because of loss of subcutaneous tissue or whether there is a real increase in size and pressure. Veins in this patient stood out prominently everywhere. Some of this was the result of great wasting of subcutaneous tissue; but they were much more prominent than one sees in patients with anorexia nervosa or the terminal stages of the cachexia of cancer. There had been some loss in the libido and potency. This had not been complete and seemed to come and go along with other variations in severity of the disease. The mechanism of gynecomastia was no clearer than it usually is. Wernicke's syndrome with lesions in the nuclei of the oculomotor nerves was strongly suggested. There was no response to subsequent protracted treatment with thiamine and other B-complex vitamins.

Conclusions

I have reported the salient features of a man who had steatorrhea, Wernicke's syndrome, phlebectasia, and vascular lipomas. It is possible that this represents a new snydrome.

Dr. J. R. Carter and Dr. J. M. Layton gave advice about the vascular lipoma, and Dr. Margaret Vance Siems helped with the studies done on the metabolism ward.

A Bibliography of Internal Medicine

Rheumatic Fever

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So much has been written on every phase of rheumatic fever that the bibliographer is confronted with an almost hopeless task. We call the reader's attention again to the fact that the present list is compiled not for specialists but for general doctors and medical students; although it is certainly incomplete, we have tried to mention every reference which deals with a really fundamental advance in knowledge of the subject.

Excellent older accounts of acute rheumatic fever are those of Senator (Polyarthritis rheumatica acuta, in von Ziemssen, H.: Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1875, Vol. 13, p. 12) and of A. Pribram (Der acute Gelenkrheumatismus, Wien, Alfred Hölder, 1901. The latter monograph, of some 500 pages, is especially comprehensive; it leaves no phase of the disease to date untouched, and it concludes with a bibliography of nearly 2000 titles. Of the numerous briefer English books should be mentioned especially that of Cheadle (Ref. 14). The monographs on the relation of streptococci to rheumatic fever (Annals of the Pickett-Thomson Research Laboratory, London, Baillière, Tindall & Cox, 1928, Vol. 4, pt. 1) contain useful bibliographies. The books by Coburn (Ref. 22) and by Wilson (Ref. 11) deal with certain special phases of the subject but are of general interest and have good bibliographies. Finally, there is assembled in a symposium on "Rheumatic Fever" (L. Thomas, Editor, Minneapolis, University of Minnesota Press, 1952), a series of recent articles which really cover the whole subject. An excellent brief summary of the disease is given by L. A. Rantz (Ref. 24).

Invaluable critical bibliographies of recent literature on rheumatic fever are included in the "Rheumatism Reviews" which have appeared under the leadership of P. S. Hench in the *Annals of Internal Medicine*, 9:883,; 1936; 10:754, 1936; 11:1089, 1938; 12:1005, 1939; 13:1655, 1940; 14:1383, 1941; 15:1002, 1941; 28:66, 1948; 39:498, 1953. To these should be added the article by C. B. Perry (Review of the Literature on Acute Rheumatism During the Years 1939-1945, *Ann. Rheumat. Dis.* 6:162, 1947).

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1. **Baillie, M.** The Morbid Anatomy of Some of the Most Important Parts of the Human Body, Ed. 2, London, J. Johnson, 1797, p. 46.

Baillie gives a good description of mitral disease: "The valvular apparatus between the auricles and ventricles is also occasionally thickened, having lost all its transparency, and having an opaque white colour. The chordae tendineae likewise become thicker than natural . . . . " (p. 32). And as to symptoms, he says: "When the heart is much enlarged, it is attended with palpitations . . . . but more commonly the pulse is feeble and irregular . . . . The causes which produce a marked growth of the heart are but little known; one of them would seem to be *rheumatism attacking this organ* [italics ours]." In a footnote, he adds: "Dr. Pitcairn has observed this in several cases."

Here then is one of the first hints of a relation of rheumatic fever and valvular heart disease. For the most part, however, no one at the time suspected such a relation. John Abernethy (On a Diminution [in Consequence of Disease] of the Area of the Aperture by Which the Left Auricle of the Heart Communicates with the Ventricle of the Same Side, *Medico-Chir. Tr.* 1:27, 1815), for example, describes accurately the clinical features and autopsy findings in two cases of mitral stenosis with no hint of "rheumatism" preceding the heart disease.

2. **Haygarth, J.** A Clinical History of Diseases: Part First: Being 1. A Clinical History of the Acute Rheumatism, London, Cadell & Davies, 1805.

In this little monograph, Haygarth gives an excellent clinical description of acute rheumatic fever. "The symptom peculiar to this disease is an inflammation of the joints which often increases to great violence, with swelling, soreness to touch, and sometimes redness of the skin. It attacks most, if not all the joints of the body in different patients, often two, three or more joints at a time, leaving some and going to others in succession, frequently returning again to each of them several times during the disease [p. 16] . . . . Exposure to cold or moisture is the chief cause of the acute rheumatism [p. 17] . . . . This very formidable and extremely painful disease continues for many weeks; more or less . . . . The remedies usually employed in the acute Rheumatism are bleeding by the lancet or leeches, blisters, antimony, sudorifics, saline medicines, and the warm Bath. The principal purpose of this publication is to recommend the Peruvian Bark in preference to all other remedies [p. 18]." For whatever it means we quote the following: "Hence we learn that persons who have been previously affected with the acute or chronical Rheumatism, the gout or *sore throat* [italics ours], especially the first are most liable to suffer attacks of this disease" (p. 30).

But throughout the book, including numerous case reports, there is not a word to indicate that the writer had any idea of an association with heart disease.

3. **Dundas, D.** An Account of a Peculiar Disease of the Heart, *Medico-Chir. Tr.* 1:37, 1815.

"There is a disease of the heart, which I apprehend is not very uncommon, no less than nine cases of it having, in the course of thirty-six years, fallen under my care. I have heard of several other cases, and yet I do not believe any account of it is to be found in any medical author." Dundas then gives a good description of what is clearly

mitral disease with auricular fibrillation. But significant is the following paragraph: "In all of the cases which I have seen, this disease has succeeded one or more attacks of rheumatic fever . . . the inflammation, pain and swelling of the extremities, after having shifted from one joint to another for many weeks, subsided; but the affection of the heart continued . . . producing in the progress of the disease, and towards its close, a considerable disposition to dropsy, under which the patient lingered for ten months. . . . All those I have seen were young persons. . . . One . . . I think can not recover; and one is apparently well, having survived the attack four years. He has had no rheumatic affection for two years and a half, but the action of the heart is still very violent, and easily increased by exercise. His recovery is attributed to a very strict adherence for a long time to a vegetable and milk diet, and great attention to avoid any considerable exertion." At autopsy cardiac enlargement was always present, and in one case "upon opening the left ventricle was found an irregular excrescence of the nature of polypus, attached to and nearly occupying the whole of one of the valvulae mitrales." Could this be an instance of bacterial endocarditis? Others were also aware of the relationship since Mr. Pemberton described a patient who "had been in his youth and indeed even to the time he was taken ill (aged 36) subject to acute rheumatism." Then comes an exquisite description of what was probably the onset of auricular fibrillation: "He was seized with a considerable pain at the heart, and a difficulty of respiration, great palpitation and great anxiety. He conceived that the smallest motion of the body would have instantly destroyed him, and this dread seemed to have totally bereft him of the power of utterance." So, too, Dr. Marcet gave an account of "two cases of translation of rheumatism from the extremities to the chest. . . . "

Dundas concludes: "The knowledge that this disease is always the consequence of, or is connected with, rheumatic affection, points out the necessity of attending to the translation of rheumatism to the chest; and shews the importance of employing very vigorous measures to remove it as soon as possible; but wherever it has made any considerable progress, I fear it will baffle every effort," words still as good today as 150 years ago. At any rate, it is clear that the relation of rheumatic fever to mitral disease was becoming common knowledge in the early 19th century.

4. **Wells, W. C.** On Rheumatism of the Heart, *Tr. Soc. Improve. M. & Chir. Knowl., London* 3:373, 1812.

Wells tries to set the record straight to date. He emphasizes the unpublished observations of Dr. David Pitcairn, who "about the year 1788, began to remark, that persons subject to rheumatism were attacked more frequently than others, with symptoms of an organic disease of the heart." He then alludes to Baillie's observations, which are certainly brief and inadequate (Ref. 1). He mentions the work of Dr. Odier,* of Geneva, and of Dr. Dundas (Ref. 3) and then reports cases of his own which are undoubtedly rheumatic valvular disease but not nearly as well described as those of Dundas. Wells clearly described subcutaneous fibroid nodules in his Case II. "Many of the tendons of the superficial muscles in this patient were studded with numerous small hard tumours, an appearance I have observed only in one other person. . . ." (see also Ref. 9).

5. **Bouillaud, J.** New Researches on Acute Articular Rheumatism in General, trans-

* Odier's book, "Manuel de médicine practique etc. par Louis Odier, Genève, J. J. Paschaud Libraire, 1803," is reviewed in detail in the *Edinburgh Medical and Surgical Journal* 2:446, 1806. The reviewer states: "Among the various symptoms which are apt to supervene on acute rheumatism, and to degenerate afterwards into a chronic complaint, Dr. Odier mentions an affection of the heart . . . Its characteristic symptoms are frequency and irregularity of the pulse, oppression and cough. It is frequently accompanied with anasarcous swellings. . . ."

lated by James Kitchen, Philadelphia, Haswell, Barrington & Haswell, 1837.†

Bouillaud's ideas of rheumatic fever were as follows: "Pain, heat, redness, tumefaction, with or without fluctuation of the affected joints—such are the local symptoms of acute articular rheumatism. . . . The pain is increased by touching and by the slightest motion. . . . Fluctuation, a sign of articular effusion, can only be well discovered in the large joints and especially in the knees. . . . Violent fever . . . accompanies above local symptoms. . . . Articular rheumatism, considered by itself and apart from various complications, shows itself with great variety both in extent and intensity. Thus as to extent, it sometimes is so slight as to be dissipated in twenty four hours; then, again, so severe as to resist whole months, unless the most energetic measures are used. . . . Whilst the acute rheumatism easily leaves one or more joints, it generally does so to invade others, whatever may be the mechanism which presides over this displacement. . . . By the acknowledgment of every observer . . . the duration of this disease is very long; the medium term being from 40 to fifty days [pp. 31-34]. The termination of acute articular rheumatism, although often of some duration, is rarely fatal. But yet endocarditis, pericarditis, pleuritis, with which it coincides, sometimes produces death [p. 35]."

It is clear then that Bouillaud had a much less complete view of rheumatic fever than we have today. He thought the disease consisted simply of acute inflammation of joints, which often spread to the heart. He believed that acute rheumatism was in the group of phlegmasias or acute inflammations. "Can any one indeed refuse the title of phlegmasia to a disease which at its height is characterized, in reference to its local symptoms, by pain, heat, swelling, and redness; and with respect to its general state by a most violent fever [p. 43]. As to the determining causes, they may be reduced, on final analysis, to one alone: viz., the impression of cold, especially when humid [p. 40]." Bouillaud also thought that fatigue was a contributory cause. The fact, however, that he and his contemporaries at times found frank pus in the joints of patients with "acute articular rheumatism" shows that they confused the disease with pyogenic arthritis, possibly gonococcal, which may well mimic rheumatic fever.

Bouillaud was a curious mixture of the new clinicopathological school and of old Galenical ideas. He recommends, following Sydenham, bleeding as an almost specific cure for rheumatic fever. In Case III, for example, the procedure consisted of the following: "First day of treatment—bleeding to six bowls in the morning and four in the evening. In the interval scarified cups over the precordial region to the extent of three bowls (in all 52 oz.). Second day four bowls; forty leeches. Third day—four bowls. Fourth day—three bowls. Fifth day—most of the joints are free from swelling; the pain and the fever have disappeared. Convalescent—soup."

Bouillaud was emphatic about the relation of rheumatic fever to heart disease. "It is, I will venture to say, a discovery worthy of some attention; to wit, the almost constant coincidence, either of endocarditis, or of pericarditis, or endo-pericarditis, with violent acute articular rheumatism. This fact . . . is of such vast importance that it constitutes, in some measure, a true revolution in the history of acute articular rheumatism" (Pref., p. III). It was following Laënnec's introduction of the stethoscope that diagnosis of valve lesions during life became possible in contrast to the anatomical diagnosis of the earlier observers (Refs. 1, 3, and 4). Bouillaud was a pioneer in physical examination of the heart (see for example his "Traité clinique des maladies du coeur," Paris, J. B. Baillière, 1835). "In auscultating the sounds of the heart, in some individuals still labouring under, or convalescing from, acute articular

† The original French edition, "Nouvelles Recherches sur le rhumatisme articulaire," Paris, 1836, was unfortunately not available.

rheumatism, I was not a little surprised to hear a strong, file, saw or bellows sound (bruit de râpe, de scie ou de soufflet), such as I had often met with in chronic or organic induration of the valves, with contraction of the orifices of the heart [p. 9]. Pericarditis exists in about one half of the patients affected with acute articular rheumatism [p. 12]. Endocarditis like pericarditis, manifests itself under the same influences as acute articular rheumatism [p. 12]. But in these phlegmasias . . . there exist nice degrees; and I acknowledge that in such cases the diagnosis is both difficult and uncertain [p. 16]." He also clearly described cases of valve lesions persisting or becoming evident long after all signs of articular rheumatism had disappeared.

Bouillaud was apparently unfamiliar with, or at least gave no credit to the earlier observers (Refs. 1, 3, and 4) on the relation of rheumatism to heart disease.

6. **See:** De la chorée: Rapports du rhumatisme et des maladies du cœur avec les affections nerveuses et convulsives, *Mém. Acad. méd., Paris* 15:373, 1850.

As early as 1821, the association of chorea with rheumatic fever was clearly recognized. James Copland (Case of Chorea, Etc., with an Account of Post-Mortem Appearances, *London M. Reposit.* 15:23, 1821), for example, states that "Pritchard, the subject of the following case, was attacked, at the age of nine years, with acute rheumatism. Soon after his recovery, chorea St. Viti supervened." Later he had another violent bout of rheumatic fever with cardiac involvement and "He had become again seized by chorea, similar, in all its symptoms, with the attack from which he had recovered fourteen months before." The patient died, and at autopsy the cord, which itself appeared normal, was surrounded with coagulable lymph and turbid serum. The interpretation of these findings is difficult. J. Roeser (Carditis unter der Form von Chorea St. Viti, *J. pract. Heilk.* 67:54, 1828) reports a child suffering from typical chorea who at death showed pericarditis and inflammation of the heart. Richard Bright (Cases of Spasmodic Disease Accompanying Affections of the Pericardium, *Medico-Chir. Tr.* 22:1 1839) describes the case of a young man whose trouble began with "general rheumatic symptoms, pains in the limbs, with puffiness and swelling of the wrists, and some other joints." When all this was subsiding "I found him labouring under the most fully marked symptoms of severe chorea. His head was constantly thrown from one side of the bed to the other. His lips were closed, and opened wtih a smacking sound, and when he desired to put out his tongue it was protruded with all the forced grimace and difficulty observed in chorea." There were signs of organic heart disease. He died, and at autopsy there was found acute pericarditis and endocarditis. Dr. Yonge, of Plymouth (Case of Cerebral Disturbance, Dependent upon Disease of the Pericardium, *Guy's Hosp. Rep.* 5:276, 1840), reports a somewhat similar case. "He states that about a fortnight since he was confined to bed by rheumatic fever, caused by exposure to night-air and damp, from falling asleep in a greve-yard, where he was watching a corpse. . . ." He then developed chorea and at death was found to have acute endocarditis. H. M. Hughes (Digest of 100 Cases of Chorea, *Guy's Hosp. Rep.* 4:360, 1846) presents a careful analysis of cases many of which were clearly associated with rheumatism and/or endocarditis.

But these case reports are insignificant in comparison with the monumental monograph of Sée, which occupies 150 quarto pages. Among the characteristics of chorea "most constant and most essential are irregular and disordered movements, almost always continuous and unmotivated, which without absolutely impairing the action of the will on the affected muscles, removes all synergism from their contractions, all precision from their efforts. . . ." Every feature of the disease is taken up in detail too great for us to review, but the section on association with rheumatism is of special

importance. In 128 cases of chorea, Sée found that 61 coincided with articular inflammation or pain. In the vast majority articular rheumatism preceded the chorea, but there were also cases concomitant or preceding the rheumatic fever. The material is well documented by references to the literature. There is a good deal of matter in this long essay which today seems irrelevant and incorrect, but the association of chorea with rheumatic fever is emphatically emphasized. The essential anatomical lesions were "phlegmasias [inflammations], pseudomembranous or purulent, of the serous membranes, especially of the pericardium or the arachnoid. . . . The anatomical findings in the acute phase are a pseudo-membranous inflammation, a serous congestion or a simple hyperaemia. In the chronic stage one finds the products of plastic lymph organized in the manner of patches, opacities, thickenings, adhesions, fibrous indurations, sometimes fibro-cartilaginous or bony." One doubts whether all these cases were simple chorea. J. Godwin Greenfield and J. M. Wolfsohn (The Pathology of Sydenham's Chorea, *Lancet* 2:603, 1922) give an excellent historical review and then report histological studies of a fatal case of chorea. They describe thrombosis of vessels, round-cell infiltration, and changes in nerve cells and conclude that chorea is "a meningo-encephalitis of rheumatic origin."

7. **Sutton, H. G.** Cases of Rheumatic Fever Treated for the Most Part by Mint Water: Collected from the Clinical Books of Dr. Gull, with Some Remarks on the Natural History of that Disease, *Guy's Hosp. Rep.* 11:392, 1865.

"In studying the treatment of acute disease it is impossible not to observe how confidently remedies, various and even opposite in their modes of action, have been recommended. . . . It is probably while endeavouring to explain the effects, so little to be expected from such different kinds of treatment, an opinion has been gradually formed that the natural course of the disease had more to do with the result than the remedy." Gull and Sutton therefore proceeded to study the natural course of the disease in patients treated only by rest and safeguarding. They noted that all the symptoms may subside in five, six, seven, or eight days, unaided by treatment. Every type of case is described: brief, long, recurrences, with and without cardiac involvement. "It would appear . . . that those cases in which the symptoms are acute tend to get well much sooner than those in which the symptoms are sub-acute. . . ."

Since mention of antecedent sore throat or respiratory infection, so much stressed today, is conspicuous by its absence in the contemporary descriptions, the following case in Sutton's report is of special interest and importance. "A young lady was suffering from sore throat; she was very subject to enlarged tonsils. Some yellow cheesy-looking substance was noted on the tonsils. She appeared depressed, and was sweating freely, but no acid odour. She was kept in bed for 3 days, then appearing much better, she was allowed to get up. . . . One day, about a month after she had had this throat affection, she complained of pain in the right knee. . . . There was pain, first in one knee, then in the other, also in the ankles, but no swelling; so she continued for eight or ten days." About the end of that time she became worse, and "A harsh grating to-and-fro murmur was heard over the heart.

"In relation to the rheumatic state, is the very important question, when we have lost all the symptoms of rheumatic fever,—has the patient lost the rheumatic condition of the system. The case of Dr. Rees would lead us to think not.

"A perusal of the above cases tends to show that the best treatment for rheumatic fever has still to be determined. . . . The cases show that too much importance has been attached to the use of medicines, especially in those acute cases where the tendency to a natural cure is the greatest."

In a subsequent number (A Second Re-

port of Cases of Acute Rheumatism, *Guy's Hosp. Rep.* 12:509, 1866), Sutton gives admirable descriptions of more cases of rheumatic fever; both these papers are preliminary to the study of Gull and Sutton (Ref. 8).

8. **Gull, W. W., and Sutton, H. G.** Remarks on the Natural History of Rheumatic Fever, *Medico-Chir. Tr.* 52:43, 1869.

In the first half of the century students of rheumatic fever devoted themselves largely to the trial of various remedies. Many papers appeared in which claims were made for the virtue of one or another form of medication. There was much special pleading and many *post hoc* fallacious conclusions. We have already pointed out Bouillaud's emphasis on bleeding as the only useful remedy (Ref. 5). D. J. Corrigan, on the other hand (Observations on the Treatment of Acute Rheumatism by Opium, *Dublin J. M. Sc.* 16:256, 1840), strongly advocated the use of opium. "The most important rule to be remembered . . . is that *full and sufficient* doses shall be exhibited." He prescribed it in increasing amounts until a beneficial effect was obtained. The first indication that the proper dose has been reached is "the statement of the patient, who in reply to an inquiry as to how he has passed the night, probably says that he has not slept, but that he is free from pain and feels comfortable." Kersten (Beiträge zur Behandlung des hitzigen Gelenk-Rheumatismus, *Deutsche Klin.* 1:16, 1849) also describes a rigid dosage scheme for opium; he was not as certain as Corrigan, however, that this treatment prevented cardiac complications. J. J. Furnivall (On the Pathology of Acute Rheumatism, and on the Prevention of Heart Disease, *Lancet* 1:304, 1844), after commenting on the obscurity which envelops the pathology of acute rheumatism, concludes that alkali is proper treatment because of the acid predominant in the system and "as a thinner of the fibrine superabounding in the blood." Innumerable other medicines and schemes of treatment had their advocates.

Soon, however, critical papers began to appear. Thomas K. Chambers (Statistics of the Treatment of Rheumatic Fever, *Brit. M. J.* 2: 237, 1863) found that patients treated with nitrate of potash remained in hospital for a mean stay of 40 days, those treated with bicarbonate of potash q. 2 h. stayed 34.3 days, those treated with "a less quantity of the same" stayed 40.0 days, and those treated without drugs stayed 30.0 days. When patients were bedded in blankets instead of in sheets, the occurrence of pericarditis and endocarditis was lower. Obviously these figures do not speak strongly for the virtue of medicines.

But Gull and Sutton approached the problem in a highly unbiased attitude. "In this paper we are desirous of bringing under the notice of the profession the particulars of a few more cases of rheumatic fever which have been treated by mint-water, or, in other words, by absolute rest and regulated diet, unaided by medicine. . . . We are now desirous of pointing out what appears to be the natural course of rheumatic fever with reference to the heart; to show in what proportion of cases the heart has become diseased when the patients were treated by mint-water; and to consider if there be any evidence to prove that the heart is more frequently involved where cases are treated by mint-water, or where treated by alkalies, lemon-juice, or by the application of blisters to the joints." They conclude emphatically that none of these methods of therapy influences the course or duration of the disease or prevents cardiac complications. "The reason why the heart did not become diseased when rheumatic fever was treated by alkalis or blisters to the joints is to be attributed not to the influence of drugs but to the natural course of the disease. . . . At present, therefore, as regards treatment, our cases seem to show that we are limited to a careful regimen of the patients. Rest, mechanical and physiological, rest in the very outset of the

disease. We ought not to wait until the rheumatic process has become well developed in the joints, for it appears to us that the heart becomes involved simultaneously with the joints, and by rest we hope to quiet the heart's action, and so prevent it becoming diseased."

Gull and Sutton's study is a model of critical approach and reasoning. It gave a sound orientation to therapy and prepared the way for the introduction of salicylates in treatment of rheumatic fever (Ref. 10).

9. Meynet, P. Rhumatisme articulaire subaigu avec production de tumeurs multiples dans les tissus fibreux périarticulaires et sur le périoste d'un grand numbre d'os, *Lyon med.* 19: 495, 1875.

Wells (Ref. 4) appears to have first made mention of "fibroid nodules," but his account is brief and inadequate. In his textbook on "Diseases of Children," 1868, Thomas Hillier, however, refers to a child with "aggravated chorea" who developed under his scalp "a number of hard round lumps, about the size of peas and horse beans; the skin moves over them, but they are firmly attached to the bone. They are neither red nor tender on pressure." Later there appeared a swellng on the inner condyle of his femur. "Dr. Jenner saw him with me and feared that these growths might be malignant," but in favor of rheumatism "is the circumstance that there is now a loud systolic murmur at the heart's apex." The boy got well, and the lumps disappeared.

But Meynet appears first to have directed special attention to subcutaneous fibroid nodules. He reports the case of a boy who had several rheumatic relapses. "Along the course of each of these tendons one found a rosary of little lumps about the size of a lentil or of a pea, hard to the touch, not painful and intimately adherent to these tendons . . . all around these joints one finds little tumors. . . . Furthermore, a point of importance to note, these nodosities appear and disappear with great speed; we have seen them so to speak spring up under our eyes from day to day and we have likewise seen them disappear. . . . Which is the native and the precise seat of these neoplasms? It is evident to us that they are due to rheumatism. . . . In our young subject it is evident that it is above all the fibrous tissues which are involved, joints, periosteum and tendons." Meynet left little to be described further as regards the clinical features. E. Troisier and L. Brocq (Les nodosités sous-cutanées éphémères et le rhumatisme, *Rev. méd. Paris* 1:297, 1881) reported another case and gave a thorough discussion of the subject. At about the same time there appeared the report of H. Hirschsprung (Eine eigenthümliche Localisation des Rheumatismus acutus im Kindesalter, *Jahrb. Kinderh.* 16: 324, 1881) in which he gave detailed reports of several cases. He concluded "The nodules must be considered as new growths of connective tissue of a chronic inflammatory sort with a tendency to necrobiosis. They are probably derived from tendons the tissues of which they resemble."

To T. Barlow and F. Warner (On Subcutaneous Nodules Connected with Fibroid Structures Occurring in Children the Subjects of Rheumatism and Chorea, *Tr. Int. Med. Cong.* 14: 116, 1881), however, goes the credit for the first detailed and comprehensive account. They gave an analysis of 27 cases and described the natural history of these nodules in great detail. A nodule was removed during life, and microscopic sections were made which showed "wavy strands of fibrous tissue, with caudate, spindle-shaped, nucleated cells and abundant vessels. It had, indeed, many of the characters of organizing granulation tissue." B. F. Massell, J. R. Mote, and T. D. Jones (The Artificial Induction of Subcutaneous Nodules in Patients with Rheumatic Fever, *J. Clin. Invest.* 16: 125, 1937) found that "the injection of the patient's own blood into the subcutaneous tissues of subjects with rheumatic fever frequently results in the appearance of subcutaneous nodules in the area injected. They are clinically indis-

tinguishable from nodules occurring spontaneously."

Every phase of the subcutaneous fibroid nodule is fully discussed in H. Keil's definitive monograph (The Rheumatic Subcutaneous Nodules and Simulating Lesions, *Medicine* 17:261, 1938), with over 300 references.

10. Maclagan, T. The Treatment of Acute Rheumatism by Salicin, *Lancet* 1:342, 1876.

"The idea of treating acute rheumatism by salicin occurred to me in November 1874. I had at that time under my care a well-marked case of the disease (Case 1) which was being treated by alkalies, but was not improving. I determined to give salicin; but before doing so, took myself first five, then ten, and then thirty grains without experiencing the least inconvenience or discomfort. . . . I gave to the patient referred to twelve grains every three hours. The result exceeded my most sanguine expectations. . . . On the following day, after 84 grains of salicin had been taken, the pulse had gone down to 100, the temperature to 99.6° (from 102.8° the previous day), a fall of over 3°, the pain and swelling of joints, but especially the pain, had much abated, the joints could be moved a little, and the patient expressed himself as being much better." Maclagan reported eight cases, with graphic charts showing striking drops in temperature. He concluded that salicin was a valuable remedy in acute rheumatic fever, that the more acute the fever, the more marked the benefit, usually within 24 to 48 hours, and that there was great relief of pain. "I shall be greatly obliged if those who try the remedy, and do not care to publish their observations, would kindly forward to me the results of their experience, be it favourable or otherwise."

At about the same time, Stricker (Über die Resultate der Behandlung der Polyarthritis rheumatica mit Salicylsäure, *Berl. klin. Wchnschr.* 13:1 and 15, 1876), no doubt independently, treated patients with acute rheumatic fever in Traube's clinic with salicylic acid. All the patients within 24 to 48 hours were freed of fever and local manifestations. He emphasized that this effect was something apart from the general antipyretic action of the drug. L. Reiss (Nachtrag zur innerlichen Anwendung der Salicylsäure, inbesondere bei dem acuten Gelenkrheumatismus, (*Berl. klin. Wchnschr.* 13:86, 1876) soon amplified Stricker's report. Meanwhile, Broadbent (Treatment of Rheumatic Fever by Salicylic Acid, *Lancet* 1:530, 1876), who was unaware of Maclagan's report but who knew of Stricker's work, reported similar excellent results. "Few diseases have had brought against them a heavier armament of drugs than has acute rheumatism. It has been stormed by alkalies and salines, attacked by acids, assaulted by perchloride of iron and by quinine, surprised by propylamine and ethylchlorüre, drained by venesection and purgatives, flooded alternately with hot and cold water, alarmed with blisters, blasted with hot air, lulled by opium and appeased by chloralhydrate. In addition to these, it has been constantly harassed by the raids of lesser foes, such as lemon juice, citric acid, belladonna and iodide of potassium . . . Salicylic acid has been shown by Stricker to be able to prevail against some cases of acute rheumatism and Dr. Broadbent's experience seems to confirm this character." In a letter to the *Lancet* (1:585, 1876) Maclagan complained that Broadbent did not grant him due priority, to which Broadbent replied with a gracious explanation (*Lancet* 1:619, 1876).

The use of salicylic acid or salicylate was promptly accepted as of real value. J. L. Miller (The Specific Action of Salicylates in Acute Articular Rheumatism, *J. A.M. A.* 63:1107, 1914) studied the length of time patients with acute rheumatic fever treated with and without salicylates remained in the hospital; 1907 patients with salicylates averaged a 32.28 days' stay, 1600 without salicylates, 33.6 days. Miller concluded, therefore, that "statistics show that patients

receiving salicylate are free from pain much earlier than those not treated. As the treated patients much more frequently relapse . . . the period of stay in the hospital . . . is the same." P. J. Hanzlik (Actions and Uses of the Salicylates and Cinchophen in Medicine, *Medicine* 5:197, 1926) presented a monumental review of the whole subject, with some 700 references.

In 1943, A. F. Coburn (Salicylate Therapy in Rheumatic Fever: A Rational Technique, *Bull. Johns Hopkins Hosp.* 73: 435, 1943) proposed the treatment of acute rheumatic fever by large doses of salicylates intravenously with control of blood levels. He thought that this method was more effective in preventing cardiac involvement than standard oral administration. The method was extensively taken up, but G. E. Murphy, (*Bull. Johns Hopkins Hosp.* 77:1, 1945) in a careful study, showed that in several patients given intravenous salicylates in large doses "characteristic rheumatic lesions developed in a variety of sites during the course of salicylate therapy." B. V. Jager and R. Alway (The Treatment of Acute Rheumatic Fever with Large Doses of Sodium Salicylate, *Am. J. M. Sc.* 211:273, 1946) were also unenthusiastic about Coburn's method, and now (1956) it seems to have dropped into disuse.

11. Goodhart, J. F. On the Rheumatic Diathesis in Childhood, *Guy's Hosp. Rep.* 25:103, 1880.

The large number of reports in the modern literature on the occurrence of rheumatic fever in families make one forget that this fact was recognized over 75 years ago. P. H. Pye-Smith (Analysis of the Cases of Rheumatism and Other Diseases of the Joints, *Guy's Hosp. Rep.* 19:311, 1874) is quite emphatic. "There can be no doubt that a tendency to rheumatic fever is inherited." He gives an analysis of 68 cases in which the patient asserted that one or more of his blood relations had been attacked by rheumatic fever. Goodhart goes into the matter much more thoroughly. "Acute rheumatism in children is in the majority of cases inherited." His paper concludes with a table of cases indicating the occurrence of rheumatic manifestations in the family. For example, of children with acute rheumatic fever we have statements such as the following: Girl, aged 9. Father has had rheumatic fever. Boy, aged 9. Mother has had rheumatic fever. Girl, aged 4. Father died with rheumatic fever. Girl, aged 4. Father died with rheumatic fever and heart disease, etc., etc. A. E. Garrod and E. H. Cooke (An Attempt to Determine the Frequency of Rheumatic Family Histories Amongst Non-Rheumatic Patients, *Lancet* 2:110, 1888) state: "It is universally admitted that rheumatism is an extremely hereditary disease." Nonetheless, the writers attempted to find out how often the relatives of non-rheumatic patients gave a history of rheumatic disease. The figure was about 20%, as against 30% to 35% in the relatives of rheumatic patients.

But Cheadle's discussion (Ref. 14, "Occasional Lectures on the Practice of Medicine," p. 227) is most impressive. "The second personal factor, viz., hereditary predisposition, is one of the most potent. . . . The tendency to rheumatism is transmitted as strongly as the tendency to gout. . . . In thirty-two consecutive cases out of my private notebooks . . . in twenty-three, that is 70 per cent, there was a definite history of rheumatic fever in near blood relations. If chorea and erythema be taken as sufficient evidence of rheumatism, the proportion is raised to . . . 93 per cent. . . . A case is recorded . . . which shows remarkable family proclivity to the disease. A rheumatic mother had twelve children, and eleven of them had rheumatism before the age of twenty . . . as might be inferred, when the proclivity is inherited from both parents the tendency is greatly intensified; not only is the liability to the disease increased . . . but its severity and persistence are increased also. . . . Now it occurred to me that this extraordinary tendency of rheumatism to develop in certain families might be due to some special faults of local-

ity or circumstances, but careful inquiry into a number of cases showed me that they arose in various localities, in members of the family when in different places and under different conditions."

During subsequent years many papers which added little were published on the same question. The recent studies of M. G. Wilson and M. D. Schweitzer (Rheumatic Fever as a Familial Disease, Environment, Communicability and Heredity in Their Relation to the Observed Familial Incidence of the Disease, *J. Clin. Invest.* 16:555, 1937) seem, however, to carry the subject further. In a careful study of families under controlled conditions, they found, as had Cheadle, that "there did not appear to be a direct relation between the environments studied and the incidence of rheumatic fever. There was no direct relation between the type and source of exposure and the resulting activity. . . . Intimate contact ('familial exposure') and casual contact ('extrafamilial exposure') were equally effective. . . . The hereditary mechanism involved was a single autosomal recessive gene." Their general conclusion is that "susceptible" persons acquire rheumatic fever much more readily than others, but they do not determine from these studies the exact role of environment and contagion in the acquisition of the disease. J. R. Paul and R. Salinger (The Spread of Rheumatic Fever Through Families, *J. Clin. Invest.* 10:33, 1931) had come to similar conclusions and thought that the spread of rheumatic fever through families strongly suggests infection, with the role of environment and hereditary predisposition as yet undetermined. It was of interest that rheumatic activity was often accompanied by evidence of respiratory tract infection. An intensive analysis of the whole problem, with full bibliography, is given by Wilson in her book (Rheumatic Fever, New York, Commonwealth Fund, 1940, p. 21). Wilson has also recently summarized her views (Heredity and Rheumatic Disease, *Am. J. Med.* 2:190, 1947).

12. Fowler, J. K. On the Association of Affections of the Throat with Acute Rheumatism, *Lancet* 2:933, 1880.

The relation of hemolytic Streptococcus sore throat to rheumatic fever is a relatively modern concept. Indeed, in the older literature one scans series after series of cases (Refs. 3, 4, and 5) without finding any allusion to sore throat at all. Senator (Die Krankheiten des Bewegungsapparatus, H.: in von Ziemssen, Handbuch der speciellen Pathologie and Therapie, Leipzig, F. C. W. Vogel, 1875, Vol. 13, p. 12) for example, in his comprehensive article makes no mention of sore throat. Sutton's case (Ref. 7) is an exception to the general rule. When attention began to be centered on the throat and tonsils, confusion arose, since sore throats are mentioned with all sorts of bacteriological findings, and in many cases rheumatic fever, on the basis of the old theory of focal infection (Billings, F.: Local infection: Its Broader Application in the Etiology of General Disease, *J. A. M. A.* 63:899, 1914), was attributed to "septic tonsils," that is to say, tonsils which were simply large and which again contained bacteria of all sorts. We should make it clear that the current view of relation of sore throat to rheumatic fever refers to a specific acute Group A tonsillitis or pharyngitis, even if mild. Much of the older literature is therefore worthless; it is comprehensively reviewed by David and Robert Thomson. (An Historical Survey of Researches on the Role of the Streptococci in Acute Articular Rheumatism or Rheumatic Fever: G. The Association of Tonsillitis with Rheumatic Fever and Its Manifestations, *Ann. Pickett-Thomson Res. Lab.* 4: (Pt. 1):56, 1928.

Fowler is, however, quite clear on the subject. "I have for some time past made it a rule in all cases of acute rheumatism . . . to inquire carefully for any history of tonsillitis or catarrh of the pharynx having preceded the attack. I was led to do this by a remark from Dr. Garrod, F. R. S. when he was attending me for a severe attack of rheumatic fever in the winter of 1874. A month before my illness I had a

sharp attack of acute tonsillitis, and Dr. Garrod told me he had noticed that the two affections were not uncommonly associated. . . . Without at present being able to give an exact percentage of cases presenting this premonitory symptom, I think I should not exaggerate if I were to put it at 80 per cent." Fowler proceeds to describe the details of 20 patients in whom a bad sore throat preceded evidence of articular rheumatism by intervals of 7 to 21 days. This paper is a masterpiece of precise reporting and leaves no doubt as to the association of tonsillitis and rheumatic fever. This association is gone into detail in the elaborate "Reports of the Collective Investigative Committee of the British Medical Association" (Ref. 13). Among 655 cases of articular rheumatism, 158 were "the subjects of tonsillitis." One patient, a woman aged 30, had three attacks of tonsillitis "each followed by acute rheumatism." A. Mantle (The Etiology of Rheumatism from a Bacterial Point of View, *Brit. M. J.* 1:1381, 1887) later noted that "Rheumatism and scarlatina were not infrequently observed in the same house, scarlatina attacking the younger members of the family, rheumatic fever the older, scarlatina usually entering the house first . . . . Acute tonsillitis had frequently been observed under the same conditions." E. Roos (Über rheumatische Angina, *Berl. klin. Wschnschr.* 31:575, 1894) comments on the lack of recognition of this association in Germany and reports a case of typical tonsillitis followed in 12 days by acute arthritis. He gives an excellent comprehensive review of the early literature on the subject, as does E. Bloch (Zur Aetiologie des Rheumatismus, *München. med. Wchnschr.* 45:445, 1898).

One of the most important points of all this work was the recognition of a latent period between the sore throat and the symptoms of rheumatic fever. Later, B. Schick (Über die Nachkrankheiten des Scharlach, *Jahrb. Kinderh.* 65:132, 1907, Ergänzungsband, p. 132) formulated the latent period between scarlet fever and its sequels as an allergic manifestation, and while he mentioned postscarlatinal "rheumatism" as one of these sequels, the evidence is that he did not identify such rheumatism with acute rheumatic fever but regarded it as a specific consequence of scarlatina. This view was challenged on good evidence by J. R. Paul, R. Salinger, and B. Zuger (The Relation of Rheumatic Fever to Postscarlatinal Arthritis and Postscarlatinal Heart Disease: A Familial Study, *J. Clin. Invest.* 13:503, 1934). Recently, E. E. Fischel (The Role of Allergy in the Pathogenesis of Rheumatic Fever, *Am. J. Med.* 7:772, 1949) has given a definitive review of this phase of the subject, with a bibliography of nearly 300 titles. J. K. Aikawa (Hypersensitivity and Rheumatic Fever, *Ann. Int. Med.* 41:576, 1954) also discusses the subject in interesting fashion.

Turning now to more modern material, J. A. Glover (Incidence of Rheumatic Disease, *Lancet* 1:199, 1930) tells of an interesting outbreak in a training school where 2000 boys lived in crowded quarters. "There was a sharp epidemic of tonsillitis, followed by an outbreak of acute rheumatism. Again we see the peak of the tonsillitis epidemic precedes the crest of the rheumatic wave by some two or three weeks." The situation was now getting "warm" as to incriminating in some way the hemolytic Streptococcus. A. F. Coburn and R. H. Pauli (Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process: I. Observations on the Ecology of Hemolytic Streptococcus in Relation to the Epidemiology of Rheumatic Fever, *J. Exper. Med.* 56:609, 1932) were among the first to go further and insist on infection with hemolytic Streptococcus. "The majority of rheumatic patients who contract hemolytic streptococcus pharyngitis experience shortly afterward a definite recrudescence of their disease. In conclusion there is a close relationship between respiratory infection with hemolytic streptococcus and activity of the rheumatic process in susceptible individuals." In another paper, Coburn and Pauli (Studies on the

Relationship of Streptococcus Hemolyticus to the Rheumatic Process: II. Observations on the Biological Character of Streptococcus Hemolyticus Associated with Rheumatic Disease, *J. Exper. Med.* 56:633, 1932) showed that the streptococci isolated from the throats of rheumatic persons were not of a single Lancefield type but fell into six antigenic groups.

W. R. F. Collis (Acute Rheumatism and Hæmolytic Streptococci, *Lancet* 1:1341, 1931) quotes Dr. F. Griffith, who investigated an outbreak of tonsillitis at a public school which was followed in several instances by primary acute rheumatism. "Griffith found that a haemolytic streptococcus of a well-defined serological type was responsible for the cases and suggested (private communication) that there might be direct aetiological connexion between this streptococcal infection and rheumatic attacks." It is of interest in this connection that recent work has shown that poststreptococcal nephritis almost always is preceded by Type 12 hemolytic streptococcal throat infection (Stetson, C. N.; Rammelkamp, C. H., Jr.; Krause, R. M.; Kohen, R. J., and Perry, W. D.: Epidemic Acute Nephritis: Studies on Etiology, Natural History and Prevention, *Medicine* 34:431, 1955). Collis himself showed in an epidemic of acute tonsillitis that "rheumatic relapses occurred in 9 out of 11 children who developed acute streptococcal infection, while similar febrile disorders not associated with the hemolytic streptococcus caused no relapse." J. A. Glover and F. Griffith (Acute Tonsillitis and Some of Its Sequels: Epidemiological and Bacteriological Observations, *Brit. M. J.* 2:521, 1931) conclude that "Infection of the throat with hemolytic streptococci produces varying clinical pictures in different persons. These include first, a symptomless infection . . .; secondly, tonsillitis; thirdly, febricula, feverish catarrh or pharyngitis, without noticeable sore throat. Any of the latter three conditions may be followed by otitis media or by acute rheumatism." Glover, in contrast to the American experience, found most cases of scarlet fever to be caused by Types 1, 2, 3, and 4. W. H. Bradley (Epidemic Acute Rheumatism in a Public School, *Quart. J. Med.* 1:79, 1932) reports on an interesting outbreak in a boys' school. "Two epidemics of rheumatism are recorded and their relation to parallel waves of hemolytic streptococcal sore throat are demonstrated: the causal streptococci being of two distinct strains." L. A. Rantz, working in the Army camps on outbreaks of acute rheumatic fever during World War II, confirmed and amplified the early observations (Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, *Arch. Int. Med.* 76:131, 1945; Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat: The Poststreptococcic State, *Arch. Int. Med.* 79:401, 1947). Rantz and his associates found that the alleged latent period between throat infection and outburst of rheumatic fever was really featured by various abnormalities. They worked out details of the streptococcal infection with reference to definition of strains, and they designated all the nonsuppurative late events as the "post-streptococcic state"; there were many other interesting findings.

While attacks of acute rheumatism are, then, so often preceded by hemolytic Streptotoccus throat infections, not all outbreaks of streptococcal tonsillitis are followed by rheumatic fever. A. L. Bloomfield and A. R. Felty (Bacteriological Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility, *Arch. Int. Med.* 32:483, 1923), for example, studied with the greatest care the clinical and bacteriological features of acute follicular tonsillitis in a closed group. During one season there were 39 cases, all caused by hemolytic Streptococcus; in not a single instance was there any evidence of rheumatic fever. So, too, A. L. Bloomfield and L. A. Rantz (An Outbreak of Streptococcic Septic Sore Throat in an Army Camp, *J. A. M. A.* 121:315, 1943) studied an outbreak of acute Streptococcus sore throat affecting several hundred sol-

diers due to Type 15 hemolytic Streptococcus. Within three weeks there was no evidence of rheumatic fever in a single man. Possibly the organisms involved were not "rheumatogenic."

13. **Whipham, T.** Reports of the Collective Investigating Committee of the British Medical Association: Report on Inquiry No. III. Acute Rheumatism, *Brit. M. J.* 1:387, 1888.

The Committee invited doctors to send in reports of cases of acute rheumatism; observations on 655 patients were received. These reports are analyzed from every conceivable standpoint and furnish a mine of information. Some of the points discussed are sex, age, occupation, class in society, habits, food, locality, atmosphere, antecedent tonsillitis, antecedent scarlet fever, chorea, influence of treatment, relapsing cases, etc., etc.

14. **Cheadle, W. B.** Harveian Lectures on the Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life, *Lancet* 1:821, 871, and 921, 1889.

We have already pointed out how the concept of rheumatic fever widened in scope from simple acute arthritis during the first three quarters of the century. It remained for someone to organize and codify all this information, and this Cheadle did in these lectures, which are a landmark in the clinical study of the subject. The material was published as a book (The Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life, London, Smith, Elder & Co., 1889) and later on in revised form in Cheadle's monograph (Occasional Lectures on the Practice of Medicine, London, Smith, Elder & Co., 1900).

Cheadle enumerates the various manifestations of the rheumatic state. Endocarditis and pericarditis, pleurisy, and tonsillitis are seen in both adults and children. Subcutaneous tendinous nodules, chorea, and exudative erythema are commoner in children. "For my present purpose I shall assume the connexion and speak of these seven phases, together with arthritis, as the rheumatic series." Each of these manifestations is systematically discussed, with illustrative case reports. "The account of the various phases of rheumatism would be incomplete without some reference to the scarlatinal affection. Articular inflammation appears now and again in the course of scarlet fever, which can in no way be distinguished from that of acute rheumatism. It is often accompanied by endocarditis or pericarditis, and sometimes by chorea." In this point of view Cheadle was far ahead of his time.

T. Duckett Jones (The Diagnosis of Rheumatic Fever, *J. A. M. A.* 126:481, 1944) later classified the various manifestations of rheumatic fever from the standpoint of value in diagnosis. He divided the criteria into major (carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum) and minor (fever, arthralgia, prolonged P-R in the electrocardiogram, preceding hemolytic streptococcal infection, previous rheumatic fever, or inactive rheumatic heart disease). These criteria have been modified by the American Heart Association (Modern Concepts of Cardiovascular Disease: Jones Criteria [Modified] for Guidance in the Diagnosis of Rheumatic Fever, 1955, Vol. 24, No. 9).

15. **Newsholme, A.** The Natural History and Affinities of Rheumatic Fever: A Study in Epidemiology, *Lancet* 1:589 and 657, 1895.

"The thesis which will be advanced and supported . . . is that rheumatic fever is a specific febrile disease, caused by . . . a pathogenic micro-organism. . . . Such a view of the causation of rheumatic fever does not cover the entire ground. Assuming that rheumatic fever only occurs when a special pathogenic micro-organism is introduced . . . its causation is by no means exhausted. It occurs chiefly or only in predisposed persons, in certain states of health, and under the influence of certain

excitants—as fatigue, injury and chill, the exact value of which in its causation will be hereafter discussed. Further, it occurs by preference at certain seasons of the year, in certain localities, or perhaps on certain soils. . . . We have to consider, on the one hand, the influences determining an individual attack of rheumatic fever; and on the other hand, the wider influences determining the extent of its varying prevalence in different countries in successive years."

A more precise statement of the problem could not be made today (1956). The following factors Newsholme regards as essential: the active infective agent, conditions of environment, and personal factors. He reviews some earlier reports on "epidemic" outbreaks but concludes: "There has, however, so far as I am aware been no wide and thorough investigation of the epidemiology of rheumatic fever." First, Newsholme traces the incidence of rheumatic fever in various hospitals through the years and concludes that there is at times a definite epidemic prevalence; then the influences of the various ancillary factors enumerated above are analyzed. Newsholme feels that the influence of heredity has been exaggerated but that injury and fatigue are definite predisposing factors and that dust perhaps has some influence. He finds also a close relationship between rainfall, level of ground water, and the amount of rheumatic fever. "There is abundant evidence of seasonal incidence of rheumatic fever."

Meanwhile, A. Hirsch (Handbuch der historisch-geographischen Pathologie Ed. 2, Stuttgart, Ferdinand Enke, 1886, Vol. 3, p. 530) gives a list of outbreaks, from which he concludes that "polyarthritis is a specific infectious disease." The subject may be pursued further in the paper of D. Seegal and B. C. Seegal (Studies in the Epidemilology of Rheumatic Fever, *J. A. M. A.* 89:11, 1927) and in that of R. M. Atwater (Studies in the Epidemiology of Acute Rheumatic Fever and Related Diseases in the United States Based on Mortality Statistics, *Am. J. Hyg.* 7:343, 1927), who concludes that "acute rheumatic fever appears to be related to the family of streptococcal infections, because of bacteriological indications, clinical resemblances and epidemiological kinship." The subject is dealt with fully and systematically by J. R. Paul (The Epidemiology of Rheumatic Fever, New York, Metropolitan Life Insurance Co., 1930; The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, New York, Metropolitan Life Insurance Co., 1943). Finally, F. F. Schwentker (The Epidemiology of Rheumatic Fever, in Rheumatic Fever, edited by L. Thomas, Minneapolis, University of Minnesota Press, 1952, p. 17), gives a precise recent review.

16. **Aschoff, L.** Zur Myocarditisfrage, *Verhandl. deutsch. path. Gesellsch.* 8:46, 1904.

William Stokes (The Diseases of the Heart and Aorta, Dublin, Hodges and Smith, 1854) clearly recognized disease of the heart muscle as of importance apart from valve lesions (pp. 109, and 113). There are also a number of hints in the early literature as to the presence of anatomical myocardial changes in cases of rheumatic fever. S. West (Analysis of 40 Cases of Rheumatic Fever, *St. Bart's Hosp. Rep.* 14:221, 1878), for example, states in regard to dilatation of the heart: "This may depend upon organic changes in the muscular tissue and in one case was proved to do so by microscopical examination" which showed that "in these white patches the muscular tissue had undergone acute granular (fatty) degeneration, its fibers being converted into granular cylinders." In James F. Goodhart's case of rapid enlargement of the heart (*Tr. Path. Soc., London* 30:279, 1879) myocardial changes were found also. "I examined sections of the muscular wall microscopically and there was a considerable quantity of interstitial cell-growth around the vessels and between muscular fasciculi." But these observations were highly rudimentary, and it was L. Krehl (Beitrag zur Pathologie der Herzklappenfehler, *Deutsches Arch. klin. Med.*

46:454, 1890) and E. Romberg (Über die Bedeutung des Herzmuskels für die Symptome and den Verlauf der acuten Endocarditis and der chronischen Klappenfehler, *Deutsches Arch. klin. Med.* 53:141, 1894) who were pioneers in emphasizing the importance of the anatomical and functional state of the myocardium apart from valve lesions. While they did not describe the specific lesion of rheumatic fever, they did stress changes in the myocardium as a result of rheumatic fever and other infections.

It was Aschoff, however, who first described the specific rheumatic lesion in the myocardium—the Aschoff body. "We succeeded in defining more closely the histological make-up of the products of inflammation and indeed in finding peculiar nodules which seem to be specific for rheumatic myocarditis. To be sure full-blown nodules were found in only two cases of recurring endocarditis, but they correspond in their situation with the cellular proliferation found in the other cases. They are regularly situated in the vicinity of small or medium blood-vessels and often show an intimate relation to the adventitia. Or there may be a lesion of all the vessel coats such as is described in arteritis nodosa. The actual nodules are very small, submiliary, and consist of the approximation of strikingly large cells with one or more abnormally large slightly indented or polyphous nuclei." He goes on in much more detail. "While in one case the nodule makes the impression of a fresh cell-proliferation in another a partial or total fibrous change can be demonstrated." Aschoff strongly supported the Leipsic school, Krehl and Romberg, in their contention that cardiac failure was due more to weakness resulting from changes in the myocardium than from valve lesions.

P. Geipel soon confirmed Aschoff's findings (Untersuchungen über rheumatische Myokarditis, *Deutsches Arch. klin. Med.* 85:75, 1905), as did C. Coombs (The Myocardial Lesions of the Rheumatic Infection, *Brit. M. J.* 8:1513, 1907), in England. Meanwhile, Aschoff (A Discussion of Some Aspects of Heart Block, *Brit. M. J.* 2:1103, 1906) described the nodules in English. E. Bracht and Wächter (Beitrag zur Aetiologie und pathologische Anatomie der Myocarditis rheumatica, *Deutsches Arch. klin. Med.* 96:493, 1909) found the nodules in three cases of definite acute rheumatism but in no patient dying of other infectious diseases. Finally, W. Thalhimer and M. A. Rothschild (On the Significance of the Submiliary, Myocardial Nodules of Aschoff in Rheumatic Fever, *J. Exper. Med.* 19:417, 1914) reviewed the literature and reported their own studies. They regarded the nodules as characteristic of rheumatic infection and even in the absence of a rheumatic history believed that the presence of Aschoff bodies signifies a previous attack of rheumatism. The nodules were found in three cases of chorea, proving the close relation of this condition to rheumatism. Thalhimer and Rothschild found the nodules most often in the walls of the left ventricle; where infection antedated death by a long period, fresh Aschoff bodies were not always in evidence, but the healed remains represented by sclerotic patches were present. C. McEwen (Cytological Studies on Rheumatic Fever: I. The Characteristic Cell of the Rheumatic Granuloma, *J. Exper. Med.* 55:745, 1932) later studied material aspirated from subcutaneous fibroid nodules by supravital stains. He concluded that the characteristic large cells "probably arise from the undifferentiated mesenchymal elements of loose connective tissue, although it is possible that endothelial cells take part in their formation in some instances. Since there is little doubt that the subcutaneous rheumatic nodules are pathologically identical with rheumatic granulomata elsewhere in the body, these conclusions are considered applicable also to the Aschoff body cells of the myocardial submiliary nodules." But the subject continues in dispute, and recently G. E. Murphy (Evidence that Aschoff Bodies of Rheumatic Myocarditis Develop from Injured Myofibers, *J. Exper. Med.* 95:319, 1952) sustained the thesis that the essential lesion appears "to be damaged muscle

fibers, their fragments, and syncitial cell masses of probable muscular origin that proliferate from beneath the sarcolemma."

Other important general articles on the Aschoff body are those of W. C. von Glahn (Auricular Endocarditis of Rheumatic Origin, *Am. J. Path.* 2:1, 1926) and of B. J. Clawson. (The Aschoff Nodule, *Arch Path.* 8:664, 1929). The latter has an extensive review of the literature.

This may also be the appropriate spot to refer to the somewhat disputed subject of rheumatic arterial lesions (Klotz, O.: Arterial Lesions Associated with Rheumatic Fever, *J. Path. & Bact.* 18:259, 1913; Pappenheimer, A. M., and Von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, *J. M. Res.* 44:489, 1924).

17. **Faber, H. K.** Experimental Arthritis in the Rabbit: A Contribution to the Pathogeny of Arthritis in Rheumatic Fever, *J. Exper. Med.* 22:615, 1915.

This time, as we have pointed out (Ref. 23), was the era of isolation of nonhemolytic streptococci from cases of rheumatic fever and the production of lesions in rabbits with them. Faber noted that in the literature, especially when strains of low virulence were used, there was a latent period between injection of organisms and occurrence of arthritis, or it might even be necessary to give more than one injection to produce disease. It occurred to him therefore that perhaps the joint needed to be prepared, or "sensitized" by a preliminary contact with the antigen before an arthritic reaction could take place. He showed experimentally that streptococci of "low virulence were frequently not able to produce arthritis at the first attack but at this time prepare the way for such an effect in a later attack." It was found that the exciting injection must be the same as that used for the sensitizing injection and, furthermore, that the preparation might be made by the introduction directly into the joint of organisms living or dead. By intravenous inoculation, without previous sensitization, it was possible to cause arthritis in rabbits only after three or more injections. An analogy between these experiments and the relapses of human rheumatic fever was suggested, as well as a further analogy with the primary lesion in human rheumatic fever.

H. F. Swift and R. H. Boots (The Question of Sensitization of Joints with Non-Hemolytic Streptococci, *J. Exper. Med.* 38:573, 1923) did not, however, confirm Faber's work. They concluded that joints of rabbits first treated with streptococci "were no more liable to involvement than were other untreated joints of the same animals."

18. **Cohn, A. E., and Swift, H. F.** Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* 39:1, 1924.

Disturbance of cardiac mechanism, especially prolongation of conduction time, occurs so frequently in rheumatic fever that Jones (Ref. 14) sets it down as one of the minor diagnostic criteria. J. Parkinson, A. H. Gosse, and E. B. Gunson (The Heart and Its Rhythm in Acute Rheumatism, *Quart J. Med.* 13:363, 1919) review the literature on disturbances of cardiac mechanism in rheumatic fever and report observations on 50 cases of their own which were studied clinically and with polygraphic tracings. They described various disorders. But Cohn and Swift first dealt with the subject comprehensively with electrocardiographic studies. They found that "in one way or other the heart was affected in 35 of 37 cases of rheumatic fever." A-V block occurred in eight cases and was the most frequent disturbance next to premature auricular contractions. Such observations have now become standard practice in the study of acute rheumatic fever) Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat: The Poststreptococcic State, *Arch. Int. Med.* 79: 401, 1947).

19. Swift, H. F. The Pathogenesis of Rheumatic Fever, *J. Exper. Med.* 39:497, 1924.

Physicians had gradually recognized the association of a variety of apparently unrelated disturbances (Ref. 14) with classical acute articular rheumatism: endocarditis, pericarditis, myocarditis, chorea, subcutaneous fibroid nodules, and other lesions. Swift, in this important paper, brought out and pictured an identity of the underlying pathological changes in all these various manifestations. "The perivascular proliferative type of lesion, resembling an infectious granuloma, explains the subacute and chronic character of the clinical symptoms in many patients with this disease. Marked exudation of serum into the periarticular tissues and of serum and cells into the joint cavities are concomitants of the acute arthritis." A short while later appeared the authoritative review of W. G. MacCallum (Rheumatism, *J. A. M. A.* 84:1545, 1925), with a brilliant description of the lesions, including the diffuse rheumatic changes in the left auricle to which he first drew attention (Rheumatic Lesions of the Left Auricle of the Heart, *Bull. Johns Hopkins Hosp.* 35:329, 1924). In 1940, Swift (Rheumatic Heart Disease: Pathogenesis and Etiology in Their Relation to Therapy and Prophylaxis, *Medicine* 19:417, 1940) developed the whole subject further. Other comprehensive reviews of the pathological changes are those of B. Sacks (Pathology of Rheumatic Fever: A Critical Review, *Am. Heart J.* 1:750, 1926), of W. C. von Glahn (The Pathology of Rheumatism, *Am. J. Med.* 2:76, 1947), and of G. E. Murphy (The Histopathology of Rheumatic Fever: A Critical Review, in Rheumatic Fever, edited by L. Thomas, Minneapolis, University of Minnesota Press, 1952, p. 28). These articles have extensive bibliographies.

20. Swift, H. F.: Rheumatic Fever, *J. A. M. A.* 92:2071, 1929.

In this masterly lecture Swift brings every phase of acute rheumatic fever—clinical variations, pathology, etiology—up to date. He touches on his own hypothesis of hypersensitivity to nonhemolytic streptococci.

21. Paul, J. R. Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* 7:383, 1928.

Paul reviews critically this whole somewhat confused and indefinite subject, and, more recently, E. E. Muirhead and A. E. Haley (Rheumatic Pneumonitis, *Arch. Int. Med.* 80:328, 1947) again go over the question and report anatomical studies of their own.

22. Coburn, A. F. The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

Modern views on rheumatic fever, at least in America, were much influenced by Coburn's book. Instead of a narrow concept of acute rheumatic fever, he looks on the disease from a wider aspect as "the rheumatic state." Thus, under this head he includes a great variety of manifestations, the significance of some of which is not generally recognized. While Coburn's spectrum is perhaps too broad, he deserves credit for expanding the older narrow limits of the disease. All sorts of material—environmental, bacteriological—are discussed in detail. Coburn also deserves credit for being one of the first to point the finger at the hemolytic Streptococcus as a specific causal agent (see also Ref. 12).

But as one goes back in the literature one usually finds that things have been said before, and it must be stated that Coburn's views on the natural history of the disease were anticipated by Cheadle (Ref. 14), who actually uses the term "the rheumatic state."

23. Lichtman, S. S., and Gross, L. Streptococci in the blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases: Based on a Study of 5,233 Consecutive Blood Cultures, *Arch. Int. Med.* 49:1078, 1932.

It was inevitable that with the advent of the bacteriological era a disease such as rheumatic fever should be regarded as due to a living agent. The long series of reports of cultivation of various organisms from patients with rheumatic fever or at autopsy is thoroughly summarized by David and Robert Thomson (An Historical survey of Researches on the Role of the Streptococci in Acute Articular Rheumatism or Rheumatic Fever, *Ann. Pickett-Thomson Res. Lab.* 4: (Pt. 1): 1, 1928), and only a few can be listed in this bibliography. Throughout the history of the subject, however, three errors constantly recur. First, there was undoubtedly often confusion between acute rheumatic fever and subacute bacterial endocarditis; streptococci isolated from cases of the latter condition were often assigned as the cause of rheumatic fever. Second, there was at the time no realization that nonhemolytic streptococci are basic members of the normal flora of the throat and bowel and that they may on occasion be isolated from the blood of healthy people. Third, it was not realized that any Streptococcus injected intravenously into rabbits in adequate dosage may produce multiple lesions of joints and of endocardium. Observations of this sort were used as arguments that organisms isolated from patients were the cause of rheumatic fever. R. I. Cole (Experimental Streptococcus Arthritis in Relation to the Etiology of Acute Articular Rheumatism, *J. Infect. Dis.* 1: 714, 1904) early pointed out the latter error. First, he reported his own work to the effect that over a three-year period cultures from blood and joint effusions in every case of rheumatic fever seen in The Johns Hopkins Hospital were sterile. He then injected into rabbits strains of streptococci from sources definitely not rheumatic and concludes: "Arthritis and endocarditis may be produced by the intravenous inoculation of rabbits with streptococci from various sources, and the results obtained are quite similar to those described as resulting from the inoculation of the so-called 'Micrococcus' or 'Diplococcus rheumaticus.' Therefore the description of a distinct variety or species of streptococci based on this property of causing endocarditis and arthritis [in rabbits], is unwarranted."

A few of the early bacteriological claims must, however, be listed because of their importance in the history of the subject. F. J. Poynton and A. Paine (The Etiology of Rheumatic Fever, *Lancet* 2:861 and 932, 1900) cultivated from blood and joints in eight cases of rheumatic fever a Gram-positive coccus with which they produced lesions in rabbits. This work drew wide attention and served for some years as a focal point for discussion of the etiology of rheumatic fever. Poynton and Paine finally embodied all their work in a volume entitled "Researches on Rheumatism" (London, J. & A. Churchill, Ltd., 1913). It is of interest that years later Poynton gave ground from his strong position, doubted that a Streptococcus was the sole cause of rheumatic fever, and suggested looking elsewhere, for example, for a filter passer (The Prevention of Acute Rheumatism, *Lancet* 2: 1000, 1924). H. F. Swift and R. A. Kinsella (Bacteriological Studies in Acute Rheumatic Fever, *Arch. Int. Med.* 19: 381, 1917) were able to cultivate nonhemolytic streptoccocci from somewhat less than 10% of typical cases of acute rheumatic fever. They conclude with the rather vague statement that "it seems evident that no type of streptococcus has been constantly associated with acute rheumatic fever." B. J. Clawson (Studies on the Etiology of Acute Rheumatic Fever, *J. Infect. Dis.* 36: 444, 1925), using large amounts of blood (50 cc.) for culture, isolated nonhemolytic streptococci from a considerable percentage of cases of acute rheumatic fever and produced lesions in rabbits. He erroneously thought that "rheumatic endocarditis and subacute bacterial endocarditis may be produced by the same agent and are but different degrees of the same process." Similarly, J. C. Small (The Bacterium Causing Rheumatic Fever and a preliminary Account of the Therapeutic Action of Its

Specific Antiserum, *Am. J. M. Sc.* 173: 101, 1927) described the isolation of "a serologically specific nonhemolytic streptococcus with distinctive biological characteristics" from blood and throats of patients with rheumatic fever; with this organism he produced the usual rabbit lesions. "We, therefore, have named this microorganism Streptococcus cardioarthritidis, and offer it upon the basis of these observations as the cause of rheumatic fever." Finally, R. L. Cecil, E. E. Nicholls, and W. J. Stainsby (Bacteriology of the Blood and Joints in Rheumatic Fever, *J. Exper. Med.* 50: 617, 1929) were able to cultivate streptococci from the blood in the amazingly high figure of 83.9% of cases. "These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the alpha or viridans type."

Interestingly enough, R. N. Nye and E. Waxelbaum (Streptococci in Infectious [Atrophic] Arthritis and Rheumatic Fever, *J. Exper. Med.* 52: 885, 1930), following Cecil, Nicholls, and Stainsby's technique with meticulous care, were unable to confirm their results.

On the other side of the argument, R. N. Nye and D. Seegal (Non-Hemolytic Streptococci and Acute Rheumatic Fever, *J. Exper. Med.* 49: 539, 1929) found that blood cultures from 25 cases of acute rheumatic fever were negative for nonhemolytic streptococci. They emphasized quite properly that nonhemolytic streptococci are invariably present in immeasurable numbers in the throats of all human beings and that their cultivation from the throats of rheumatic fever patients is meaningless. "The foregoing facts seem to invalidate the assumption that any of these non-hemolytic streptococci play a specific role in the etiology of acute rheumatic fever." Another blow was struck by L. Gross, L. Loewe, and B. Eliasoph (Attempts to Reproduce Rheumatic fever in Animals, *J. Exper. Med.* 50: 41, 1929), who claimed that streptococci isolated from rheumatic fever did not produce true lesions of the disease (Aschoff bodies) in rabbits. "Judged by these criteria, we have failed to reproduce the disease. This conclusion, we believe, holds true for all the work thus far reported in the literature." It remained for Lichtman and Gross, with a truly devastating attack, to demolish the theory that rheumatic fever was a direct infection with nonhemolytic streptococci. They began by listing 11 major fallacies in the previous work and conclude that "study of 5,233 consecutive blood cultures shows [that] . . . an incidence of non-hemolytic streptococcemia between 4 and 15.5 per cent occurs in at least 9 diseases," some of which, such as aplastic anemia, anemia, leukemia, and colitis, obviously have nothing to do with rheumatic fever. "On the basis of the incidence of the 'transient' streptococcemia alone, these organisms cannot justifiably be considered causative agents of these diseases."

Thus, at long last, the ghost of this controversy which had been waged for 40 years was finally laid.

24. Myers, W. K., and Keefer, C. S. Antistreptolysim Content of the Blood Serum in Rheumatic Fever and Rheumatoid Arthritis, *J. Clin. Invest.* 13:155, 1934.

Since hemolytic streptococcal throat infections were often found to precede bouts of acute rheumatic fever, it was natural to look for antibodies against streptococci or their products in the blood serum of patients. B. Schlesinger and A. G. Signy (Precipitin Reactions in the Blood of Rheumatic Patients Following Acute Throat Infections, *Quart. J. Med.* 2:255, 1933), for example, studied precipitin reactions, and C. S. Keefer, W. K. Myers, and T. W. Oppel (Streptococcal Agglutinins in Patients With Rheumatoid (Atrophic) Arthritis and Acute Rheumatic Fever, *J. Clin. Invest.* 12:267, 1933) measured agglutinins. The determination of antistreptolysin titer has remained the popular method, however, of investigating antibodies against hemolytic Streptococcus. E. W. Todd (Antihæmolysin Titres in Hæmolytic Streptococcal Infections and Their Significance in

Rheumatic Fever, *Brit. J. Exper. Path.* 13:248, 1932) made early studies, as did A. F. Coburn and R. Pauli (Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process: III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, *J. Exper. Med.* 56: 651, 1932). Both of these groups of workers found increased titers of antistreptolysin during acute attacks of rheumatic fever. The observations of Meyers and Keefer are, however, of special interest because of the large number of controls. Thus they found that the antistreptolysin serum levels of patients with rheumatic fever fell in the same range as those with overt hemolytic streptococcal infections, such as scarlet fever and erysipelas, and that these levels were often higher than ever attained in normal persons. However, many patients with rheumatic fever had titers not above those reached in normals. J. J. Bunim and C. McEwen (The Antistreptolysin Titer in Rheumatic Fever, Arthritis and Other Diseases, *J. Clin. Invest.* 19:75, 1940) found that the "incidence of elevated titers bore no relation to the various clinical manifestations of rheumatic infection," but those whose illness was preceded by a memorable upper respiratory infection showed a response more commonly than those without such a history.

Through the years stress has been placed on abnormally high titers as an indication of hemolytic streptococcal infection or of rheumatic fever in doubtful cases where there is no overt sore throat or positive culture for a hemolytic Streptococcus. L. A. Rantz (Rheumatic Fever, Chicago, The Year Book Publishers, Inc., 1954) finds antistreptolysin measurements most useful for the exclusion of rheumatic fever: "It is evident that titers of 50 units or less are virtually incompatible with the early stages of rheumatic fever." Rantz and his group have reported other important studies on antistreptolysin (Rantz, L. A.; Maroney, M., and Di Caprio, J. M.: Antistreptolysin O Response Following Hemolytic Streptococcus Infection in Early Childhood, A. M. A. Arch. Int. Med. 87:360, 1951; Rantz, L. A.; Randall, E., and Rantz, H. H.: Antistreptolysin "O": A Study of this Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man, *Am. J. Med.* 5:3, 1948). Numerous other antistreptococcal antibodies have been studied to the same general effect, but their use has not yet become feasible in routine clinical work (Rantz, L. A.: The Prevention of Rheumatic Fever, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 16 et seq.). The earlier work is also reviewed by Wilson (Rheumatic Fever, New York, Commonwealth Fund, 1940, p. 96 et seq.). Other serological tests, not including streptococcal antibodies, have been suggested. Their use is reviewed by M. McCarty (Present Status of Diagnostic Tests for Rheumatic Fever, *Ann. Int. Med.* 37:1027, 1952). A penetrating analysis of this phase of the subject is also given by H. F. Swift (The Etiology of Rheumatic Fever, *Ann. Int. Med.* 31:715, 1949), by R. A. Good (Acute-Phase Reactions in Rheumatic Fever, in Rheumatic Fever, edited by L. Thomas, Minneopolis, University of Minnesota Press, 1952, p. 115), and by M. McCarty (The Immune Response in Rheumatic Fever, in Rheumatic Fever, edited by L. Thomas, Minneopolis, University of Minnesota Press, 1952, p. 115).

Recently stress has been placed on tests which may reveal "activity" of the rheumatic process. Such a test is the measurement of C-reactive protein in the blood. G. H. Stollerman, S. Glick, D. J. Patel, I. Hirschfeld, and J. H. Rusoff (Determination of C-Reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever, *Am. J. Med.* 15:645, 1953) and R. J. Roantree and L. A. Rantz (Clinical Experience with the C-Reactive Protein Test, A. M. A. Arch. Int. Med. 96:674, 1955) attempt to evaluate this test, upon which the last word is not yet said. The subject is summarized editorially by J. J. Bunim (Laboratory Tests for Rheumatic Activity, Editorial, *J. Chron. Dis.* 3:230, 1956).

25. Coburn, A. F., and Moore, L. V. The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Special Reference to Rheumatic Fever, *J. Clin. Invest*, 18:147, 1939.

Having found that sulfanilamide used prophylactically prevented the development of induced hemolytic streptococcal infections in guinea pigs, even though it did not cure them when established, it occurred to Coburn and Moore to see whether the drug had any prophylactic effect against rheumatic fever in children. Seventy-nine of eighty rheumatic children escaped "hemolytic streptococcal infection and signs of rheumatic activity" while under treatment. C. B. Thomas and R. France (A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull. Johns Hopkins Hosp.* 64:67, 1939) and C. B. Thomas, R. France, and F. Reichsman (The Prophylactic Use of Sulfanilamide, in Patients Susceptible to Rheumatic Fever, *J. A. M. A.* 116:551, 1941) reported similar favorable results. No major rheumatic episodes occurred during the 79 person-seasons in the treated group, whereas there were 10% recurrences in the controls. A. G. Kuttner and G. Reyersbach (The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, *J. Clin. Invest.* 22:77, 1943) strongly supported the above findings, as did R. H. Feldt (Sulfanilamide as a Prophylactic Measure in Recurrent Rheumatic Infection: A Controlled Study Involving 131 "Patient-Seasons," *Am. J. M. Sc.* 207:483, 1944). Masseloff and Robbins (Prophylactic Use of Sulfonamides in Children with Rheumatic Fever, *J. Lab. & Clin. Med.* 28:1323, 1943), on the other hand, failed to find a significant difference between the test group and the controls. A. J. Morris, R. Chamovitz, F. J. Catanzaro, and C. H. Rammelkamp Jr. (Prevention of Rheumatic Fever by Treatment of Previous Streptococcic Infections: Effect of Sulfadiazine, *J.A.M.A.* 160:114, 1956) found that the treatment of the acute sore throat with sulfadiazine neither eradicated the Streptococcus nor prevented subsequent rheumatic fever. However, they regarded sulfonamides as of value in prophylaxis.

All of this work has now become rather a dead issue since sulfonamides have been almost universally replaced by penicillin (Ref. 27), but it served to bring out a principle in the prophylaxis of rheumatic fever which is generally recognized as sound —the prevention of hemolytic Streptococcus throat infections protects against the evidences of rheumatic fever which so often follow such infection.

26. Rich, A. R., and Gregory, J. E. Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, *Bull. Johns Hopkins Hosp.* 73:239, 1943.

We have already referred to the concept of hypersensitivity in rheumatic fever (Ref. 12). The observations of Rich and Gregory seem, however, particularly striking. "The experimental procedure in this study has consisted in the sensitization of rabbits to sterile horse serum, under conditions that produce serum sickness." They picture beautiful lesions that "in their basic characteristics, resemble closely those of rheumatic carditis." In a further paper, Rich and Gregory (Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity *Bull. Johns. Hopkins. Hosp.* 75:115, 1944) show side-by-side experimental lesions and the lesions of human rheumatic carditis; they appear practically identical. S. D. Kobernick (Experimental Rheumatic Carditis, Periarteritis Nodosa and Glomerulonephritis, *Am. J. M. Sc.* 224: 329, 1952) gives a comprehensive review of the entire subject, with full bibliography.

27. Massell, B. F., Dow, J. W., and Jones, T. D. Orally Administered Penicillin in Patients with Rheumatic Fever, *J. A. M. A.* 138:1030, 1948.

The authors report pioneer observations of the effect of penicillin on hemolytic Streptococcus carriage in the throat. Orally administered penicillin in doses of 300,000 to 1,000,000 units per day for 10 days suppressed hemolytic streptococci in the throats of all but 2.1% of patients with rheumatic fever. Many papers soon followed describing all sorts of permutations and combinations of methods of administration, dosage, and type of preparation of penicillin. Some of the important reports are the following: F. W. Denny, L. W. Wannamaker, W. R. Brink, C. H. Rammelkamp Jr., and E. A. Custer (Prevention of Rheumatic Fever, *J.A.M.A.* 143:151, 1950); L. W. Wanamaker, C. H. Rammelkamp Jr., F. W. Denny, W. R. Brink, H. B. Houser, E. O. Hahn, and J. H. Dingle (Prophylaxis of Acute Rheumatic Fever, by treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin, *Am. J. Med.* 10:673, 1951); B. F. Massell, G. P. Sturgis, J. D. Knobloch, R. B. Streeper, T. N. Hall, and P. Norcross (Prevention of Rheumatic Fever by Prompt Penicillin Therapy of Hemolytic Streptococcic Respiratory Infections, *J.A.M.A.* 146:1469, 1951); B. B. Breese, chairman (Prevention of Rheumatic Fever, Modern Concepts of Cardiovascular Disease, 1953, Vol. 22, No. 1); R. L. Chancey, A. J. Morris, R. H. Conner, F. J. Catanzaro, R. Chamovitz, and C. H. Rammelkamp Jr. (Studies of Streptococcal Prophylaxis: Comparison of Oral Penicillin and Benzanthine Penicillin, *Am. J. M. Sc.* 229:165, 1955), and, finally, G. H. Stollerman, J. H. Rusoff, and I. Hirschfeld (Prophylaxis Against Group A Streptococci in Rheumatic Fever, *New England J. Med.* 252:787, 1955). Stollerman observed no recurrences among 145 patients with rheumatic fever who received monthly injections of benzanthine penicillin during a two-year period. As a result of all of this work the various heart associations are now urging that children who have had evidence of rheumatic fever receive penicillin prophylaxis over long periods. The final details of this procedure are not yet defined.

The whole subject of prevention of rheumatic fever is critically discussed in L. A. Rantz (The Prevention of Rheumatic Fever, Springfield, Ill., Charles C Thomas, Publisher, 1952).

28. Murphy, G. E., and Swift, H. F. Induction of Cardiac Lesions, Closely Resembling Those of Rheumatic Fever, in Rabbits Following Repeated Skin Infections with Group A Streptococci, *J. Exper. Med.* 89:687, 1949.

Although Faber's views (Ref. 17) demand some modification in the light of recent work, he deserves credit for opposing the idea that rheumatic fever was a simple direct infection with streptococci and promoting the concept of altered reactivity (allergy) in the mechanism of production of the clinical phenomena of the disease.

We must now turn to the work of Swift, since it dominated the stage in America at least for many years. He too regarded hypersensitivity as implicit in the reaction of rheumatic fever and with his associates developed a hypothesis which they formulated as follows: "The theory is advanced that the pathogenesis of rheumatic fever can be explained by the existence in certain individuals of a condition of hypersensitiveness (allergy or hyperergy) to streptococci resulting from repeated low-grade infections or from the persistence of foci of infection in the body. When under suitable circumstances streptococci or products of streptococci are disseminated to the tissues these tissues over-react and the characteristic picture of the disease results." (Swift, H. F.; Derick, C. L., and Hitchcock, C. H., Rheumatic Fever as a Manifestation of Hypersensitiveness [Allergy of Hyperergy] to Streptococci, *Tr. A. Am. Physicians* 43:192, 1928). In another paper (Bacterial Allergy [Hyperergy] to Nonhemolytic Streptococci, in Its Relation to Rheumatic Fever, *J.A.M.A.* 90:906, 1928), these writers further set forth their hypothesis and express the feeling that in their experiments reactions which have been ascribed to hemolytic streptococci have not been obtained.

It would serve no purpose to give in detail the analogies with syphilis and tuberculosis upon which Swift's hypothesis was based or to recite the experimental evidence with which Swift and his associates sought to support their views during the next decade. A list of the principal papers is as follows: C. L. Derick and H. F. Swift: Reaction of Rabbits to Non-Hemolytic Streptococci: I. General Tuberculin-like Hypersensitiveness, Allergy or Hyperergy Following the Secondary Reaction, *J. Exper. Med.* 49: 615, 1929; C. H. Hitchcock and H. F. Swift: Studies on Indifferent Streptococci: III. The Allergizing Capacity of Different Strains, *J. Exper. Med.* 49:637, 1929; H. F. Swift and C. L. Derick: Reactions of Rabbits to Non-Hemolytic Streptococci: II. Skin Reactions in Intravenously Immunized Animals, *J. Exper. Med.* 49:883, 1929; H. F. Swift, C. H. Hitchcock, C. L. Derick, and Currer McEwen: Intravenous Vaccination with Streptococci in Rheumatic Fever, *Am. J. M. Sc.* 181:1, 1931; C. L. Derick and M. N. Fulton: Skin Reactions of Patients and Normal Individuals to Protein Extracts of Streptococci, *J. Clin. Invest.* 10:121, 1931; M. P. Schultz and H. F. Swift: Reactions of Rabbits to Streptococci: Comparative Sensitizing Effect of Intracutaneous and Intravenous Inocula in Minute Doses, *J. Exper. Med.* 55:591, 1932.

The obvious error in interpretation of this work is that while Swift and his associates clearly produced evidence of allergic reactions to nonhemolytic streptococci and their products, they did not produce rheumatic fever.

But by 1940 Swift seems to have modified his views on relation of nonhemolytic Streptococcus to rheumatic fever (Rheumatic Heart Disease: Pathogenesis and Etiology in their Relation to Therapy and Prophylaxis, *Medicine* 19:417, 1940). He now inclines to the hemolytic Streptococcus as the causal agent. "At present the hemolytic streptococcus seems to bear a more intimate relationship to the disease than any other known pathogenic agent." He refers to outbreaks of tonsillitis followed by rheumatic fever (Ref. 12). Later, Swift (The Relationship of Streptococcal Infections to Rheumatic Fever, *Am. J. Med.* 2:168, 1947) speaks out even more strongly for hemolytic Streptococcus on the basis of patients with scarlet fever who later developed evidence of rheumatic fever. The investigations of Swift culminated in his important work with Murphy. They found that rabbits after sustaining 2 to 10 infections with hemolytic streptococci of different serological types within 3 to 20 months sickened and developed various symptoms. "In the hearts of the . . . infected rabbits . . . there have been found on microscopic examination focal alterations in the connective tissue framework in blood vessel adventitia, valves, mural endocardium, epicardium and in the myocardial interstitium." These and other lesions "closely resembling those found in rheumatic fever, have developed in rabbits that sickened following multiple successive skin infections with several serological types of Group A steptococci." The lesions are beautifully pictured. Finally, a most interesting report is that of R. J. Glaser, W. A. Thomas, S. I. Morse, and J. E. Darnell Jr. (The Incidence and Pathogenesis of Myocarditis in Rabbits After Group A Streptococcal Pharyngeal Infections, *J. Exper. Med.* 103:173, 1956). These workers devised a method of producing acute streptococcal pharyngeal infections in rabbits, which in many cases were followed by myocardial lesions which were thought typical of rheumatic fever. When intradermal infections with the same organism were produced, the lesions appeared in a much smaller number of animals.

29. Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C. The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on Acute Phase of Rheumatic Fever: Preliminary Report, *Proc. Staff Meet. Mayo Clin.* 24:277, 1949.

Hench and his associates first observed

that cortisone had favorable effects on rheumatic fever. This brief report was promptly followed by extensive use both of cortisone and of corticotropin (ACTH) in other cases of the disease. Within a year it was possible for B. F. Massell, J. E. Warren, G. P. Sturgis, B. Hall, and E. Craige (The Clinical Response of Rheumatic Fever and Acute Carditis to ACTH, *New England J. Med.* 242:641, 1950) to make an extensive report on the subject. In general, the results were favorable, although on long usage the untoward effects of adrenal steroids manifested themselves. Reports now came in rapidly; some of the important ones were the following: M. G. Wilson and H. N. Helper (Effect of Pituitary adrenocorticotropic hormone [ACTH] in Acute Rheumatic Carditis, *J.A.M.A.* 145:133, 1951); T. N. Harris, W. B. Abrams, T. F. P. Leo, and J. P. Hubbard (Cortisone Therapy in Acute Rheumatic Carditis: Preliminary Observations, *Circulation* 3:215, 1951); A. G. Kuttner, J. S. Baldwin, C. McEwen, J. J. Bunim, M. Ziff, and D. K. Ford (Effect of ACTH and Cortisone on Rheumatic Carditis, *J.A.M.A.* 148:628, 1952), and A. R. Barnes (The Effects of Cortisone and ACTH on the Acute Phase of Rheumatic Fever, *Circulation* 3:770, 1951). A. Golden and J. W. Hurst (Alterations of the Lesions of Acute Rheumatic Myocarditis During Cortisone Therapy, *Circulation* 7:218, 1953) reported the changes in the cardiac lesions of a patient dying with acute rheumatic heart disease treated with cortisone. An inhibition of the inflammatory reaction was found without demonstrable alteration of the collagen injury. So, too, L. M. Taran, G. A. Gulotta, N. Szilagyi, J. M. Jablon, and W. K. Lane (Effect of Cortisone and ACTH on the Protracted Phase of Rheumatic Carditis in Children, *Am. J. Med.* 14:275, 1953) found that the exudative manifestations responded readily so long as therapy was maintained, but there was no convincing indication of definite arrest of active carditis. B. H. Massell (Medical Progress: ACTH and Cortisone Therapy of Rheumatic Fever and Rheumatic Carditis, *New England J. Med.* 251:183, 221, and 263, 1954) carefully reviews the entire literature to date. He points out that the original hope of a total rapid cure of rheumatic fever by steroid therapy is not to be realized, whereas a suppression of various inflammatory components of the disease may be achieved—especially fever and polyarthritis. Finally, a report by the United Kingdom and United States cooperative group (The Treatment of Acute Rheumatic Fever in Children: A Cooperative Clinical Trial of ACTH, Cortisone and Aspirin, *Circulation* 11:343, 1955) concludes that "There was no evidence that any of the three agents resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment. . . . At the end of one year there was no significant difference between the three treatment groups in the status of the heart." The use of steroids is therefore (January, 1956) still *sub judice.*

30. **Pinniger, J. L.** The Left Auricular Appendage in Mitral Stenosis: A Study of 15 Cases Submitted to Valvulotomy, *St. Thomas's Rep.* 7:(Ser. 2):54, 1951.

It had come to be generally accepted that the Aschoff body was not only evidence of the "rheumatic state," but that "fresh"-looking nodules indicated an "active" stage of the disease. With the development of mitral valvulotomy for mitral stenosis, there came into vogue the excision of the tip of the auricular appendage, partly for purposes of biopsy. Pinniger was the first to report examinations of auricular appendages removed at operation. "Aschoff node formation was present . . . in no fewer than 10 (65 per cent) of these cases. These findings give strong support to the view that activity of the rheumatic process persists in a high proportion of patients with clinically quiescent rheumatic valvular disease." A little later M. Kuschner, M. I. Ferrer, R. M. Harvey, and R. H. Wylie (Rheumatic

Carditis in Surgically Removed Auricular Appendages, *Am. Heart J.* 43:286, 1952), in appendages excised in 11 patients who were clinically regarded as definitely inactive, found Aschoff bodies in 4. D. Sabiston and R. H. Follis Jr. (Lesions in Auricular Appendages Removed at Operations for Mitral Stenosis of Presumed Rheumatic Origin, *Bull. Johns Hopkins Hosp.* 91:178, 1952) made similar studies of the material from Blalock's clinic and also found the histological changes of rheumatic fever in a number of cases. "Of particular significance would appear to be the discovery of such changes in patients who did not give a history of ever having had symptoms of a rheumatic episode." Similarly, J. P. Decker, C. Van Z. Hawn, and S. L. Robbins found Aschoff bodies in 83 of 183 excised auricular appendages (Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis: I. Anatomic Aspects, *Circulation* 8:161, 1953). Review of the clinical records of these patients by W. F. McNeely, L. B. Ellis, and D. E. Harken (Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis: II. Clinical Aspects *Circulation* 8:337, 1953), showed no correlation between presence of Aschoff bodies and the usual clinical or laboratory criteria of rheumatic activity. Finally, J. R. Gil, H. Rodriguez, and J. J. Ibarra (Incidence of Asymptomatic Active Rheumatic Cardiac Lesions in Patients Submitted to Mitral Commissurotomy and the Effect of Cortisone on These Lesions, *Am. Heart J.* 50:912, 1955) concluded from similar findings that "a large group (60 per cent) of patients submitted to commissurotomy show active but asymptomatic rheumatic cardiac lesions."

But is there not another possible interpretation of all of these findings? If Aschoff bodies are frequently found in patients with no evidence of rheumatic activity, are the nodules absolutely reliable evidence of such activity? This thought would seem to be supported by the observations of W. A. Thomas, J. H. Averill, B. Castleman, and E. F. Bland (The Significance of Aschoff Bodies in the Left Atrial Appendage, *New England J. Med.* 249:761, 1953), who found that "The Aschoff lesions and other histological changes in the atrial appendage of patients with fatal rheumatic fever are identical with those found in the surgical specimens from patients with mitral stenosis who show no recognizable clinical or laboratory signs of recent rheumatic activity," even though the authors themselves draw the opposite conclusion.

31. Soloff, L. A.; Zatuchni, J.; Janton, O. H.; O'Neill, T. J. E., and Glover, R. P. Reactivation of Rheumatic Fever Following Mitral Commissurotomy, *Circulation* 8:481, 1953.

The writers give a systematic description of the "postcommissurotomy" syndrome. The syndrome occurred in 24% of 179 consecutive persons subjected to the operation. It is characterized by precordial pain and by fever, is frequently associated with the precipitation or intensification of heart failure, and is at times accompanied by migratory joint pains, arrhythmias, hemoptysis, or psychosis and sometimes terminates in death. The writers give arguments in favor of this syndrome being rheumatic activation and speculate as to the exact mechanism of action.

Proctosigmoidoscopy in the General Physical Examination

An Analysis of 5158 Examinations

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Since the purpose of the physical examination is to discover disease, it would seem logical to stress those techniques which detect the most frequent and most serious diseases in their earliest stages. An exception to this generally accepted approach is the relative neglect of the proctosigmoidoscopic examination.

In a recent study of a large tumor registry,[1] carcinoma of the rectum and colon was the most frequently encountered cancer. It has been amply demonstrated that these often develop from adenomatous polyps and that from two-thirds to three-fourths of these cancerous and precancerous lesions occur within reach of the 25 cm. sigmoidoscope. In spite of the significance of this well-documented knowledge, we believe proctosigmoidoscopy is the most neglected of the simple diagnostic procedures.

The technique of this simple procedure is seldom taught to medical students. Interns and residents who display remarkable erudition of the more glamorous radioisotopes, cardiac catheterization, and flame photometers have often never seen or done a simple proctosigmoidoscopic examination. To be sure, routine digital examination of the rectum has been taught for more than two generations, but, for the proper examination of this area, the finger is an inadequate instrument.

Surgeons and gastroenterologists have recognized the importance of proctosigmoidoscopy for more than two decades. Indeed, a slogan of the American Cancer Society is "Polyp detection is cancer prevention." Nevertheless, internists and general practioners, upon whom early diagnosis often depends, continue to neglect it. Many outstanding medical centers still do not include the procedure as an integral part of the general physical examination.

It is the purpose of this paper to demonstrate statistically that, in the adult male, rectosigmoidal polyps are common; that polyp detection is frequently cancer detection; that polyp detection is more frequently cancer prevention when the adenomatous polyps are removed; that the only accurate method of polyp detection is proctosigmoidoscopy, and that this procedure should be a part of every complete physical examination.

Materials and Methods

The Greenbrier Clinic is a diagnostic medical clinic. Approximately two-thirds of the patients are examined under company-sponsored executive health programs. A proctosigmoidoscopic examination has been a part of the general physical examination of male patients since the clinic was founded. It is apparent that this approaches a truly unselected group, since these are not hospital patients, nor have they consulted a physician because of symptoms.

Proctosigmoidoscopy is performed by the internist at the time of the physical examination. Most examinations are in the morning. If the patient has had a morning bowel movement, frequently no further preparation is needed. If feces are encountered, a low enema of sodium biphosphate and sodium phosphate (Phospho-Soda) solu-

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tion is administered from a disposable plastic bottle. This results in excellent preparation in nearly all patients with very little loss of time. We feel that the customary procedure of having all patients administer enemas to themselves is an imposition when less than half need enema preparation after a normal bowel movement. A self-administered enema is to some an unpleasant experience. Perhaps our approach to preparation is one reason that patient acceptance has been 100%.

An attempt was made in each case to pass the sigmoidoscope as far as safely possible. Quite frequently it was impeded at 16-17 cm. by angulation or spasm of the bowel.

Through July 31, 1955, a total of 5158 examinations were performed on 2401 men. Table 1 demonstrates that many have had several examinations, a few as many as seven. Ages ranged from 32-80 years, with a mean age of 53 years. There have been no untoward reactions in this series.

TABLE 1.—*Incidence of Polyps Discovered by 5,158 Proctosigmoidoscopic Examinations of 2,401 Patients*

	No. of Patients Examined	No. of Patients with Polyps (%)
Annual Examination		
1st	2401	94 (3.9)
2nd	1183	43 (3.6)
3rd	764	19 (2.5)
4th	450	10 (2.2)
5th	225	5 (2.2)
6th	87	2 (2.3)
7th	48	1 (2.1)
Total no. examinations	5158	161 (6.7 total patients) (3.1 total examinations)

Results

Rectal and/or sigmoidal polyps were discovered in 161 patients (6.7% of patients examined, 3.1% of the total examinations).

Reference to Table 1 reveals that, as expected, polyps are most likely to be discovered on the first examination (3.9%). Of course, the first examination here was not actually the first examination for many, since an appreciable number had been sigmoidoscoped elsewhere during previous examinations. We do not have accurate information as to the number previously examined.

A high yield was also obtained on the second annual examination. Thereafter, there is an almost constant find of slightly more than 2% on each subsequent annual examination.

Fourteen patients had polyps on subsequent examinations after previously discovered polyps had been removed.

In 113 instances the polyps were solitary, but in 48 from two to "many" were observed. The actual number of multiple polyps is higher, since in many instances the proctologist to whom the patient was referred found additional polyps.

They were located from 3 to 25 cm. from the anal margin. The average depth was 12.2 cm. Only 40 (25%) were less than 10 cm. Only four were felt on digital examination of the rectum!

Of the 161 patients, 17 (10.6%) gave a history of rectal bleeding. A review of the histories suggests that in some of these the bleeding was most probably hemorrhoidal.

All patients with polyps were urged to consult a proctologist for removal of the neoplasms. We have heard from the doctor or patient in 88 instances. Since many surgeons fulgurate small polyps without biopsy and since follow-up is difficult, we

Fig. 1.—Typical, benign, adenomatous rectal polyp.

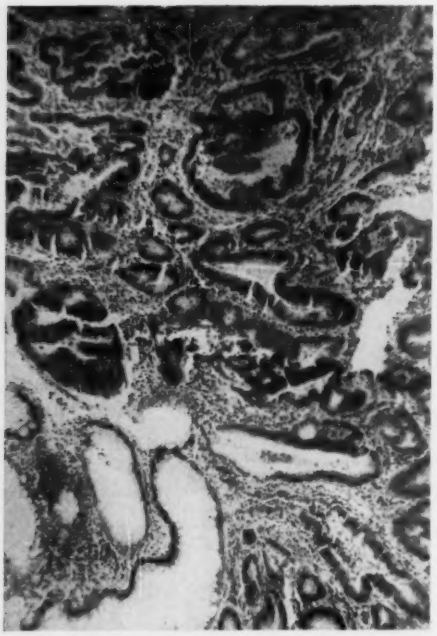

Fig. 2.—Invasive carcinoma of the rectum discovered on routine examination of a completely asymptomatic patient.

Fig. 3.—Carcinoma in situ in a rectal polyp.

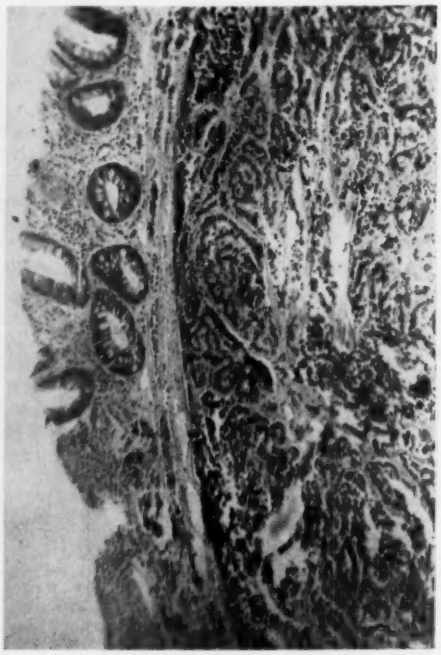

Fig. 4.—A rectal polyp containing carcinoid.

have received direct or indirect pathologic reports in only 53 instances; 36 were said to be benign adenomatous polyps (Fig. 1); 8 contained invasive carcinoma (Fig. 2); 8 others were reported as "carcinoma in situ," "hyperplastic polyps," or "atypical hyperplasia" (Fig. 3); one was a carcinoid, not rare in the appendix and lower ileum but quite unusual in the rectum (Fig. 4).

Double-contrast barium-enema studies were made in 110 of the 161 patients in whom rectal or sigmoidal polyps were discovered. Fourteen (12.7%) had definite polyps at a higher level in the colon (Fig. 5); six had probable small polyps; one had an annular carcinoma. It is currently the policy of this Clinic to obtain such studies on every patient in whom polyps are discovered.

Of particular interest is the fact that three cases of previously unsuspected multiple polyposis of the colon were discovered by the combination of routine proctosigmoidoscopy with follow-up double-contrast barium-enema studies (Fig. 6). A case of

Fig. 5.—A sigmoidal polyp on a stalk in an asymptomatic patient. The double-contrast barium-enema study was made because a small rectal polyp was discovered by routine proctosigmoidoscopy.

Fig. 6.—Multiple polyposis of the colon in a 51-year-old man, discovered by routine proctosigmoidoscopy. Only a small fraction of the polyps are marked with arrows.

multiple polyposis associated with pigmentation of the lips in a woman is reported elsewhere.[2]

Fifty-three patients with polyps had a history of carcinoma in the immediate family; seventeen were known to be intestinal carcinomas, twenty-five involved other organs, and in eleven the patient did not know the origin of the cancer in his relative.

Comment

Incidence of Polyps of the Rectum and Sigmoid

Various authors have found the incidence of polyps of the rectum and colon to vary from 2.3% to 12.3%, depending on the material studied and method of study (3-15). They are commoner in men than women, and their frequency is proportionately related to age.*

We believe the incidence in our patients has special significance because it is one of the largest series and because of the freedom from selection. To our knowledge, the only other report of routine examinations of executives consists of 50 patients, a series too small to be statistically significant.

Our results approximate the average of those found in other large series, particularly those in the large cancer-detection clinics.† They are almost identical with the largest series.[11] We had anticipated that the incidence in our group would be lower because of absence of selection. We reasoned that many patients are motivated to visit diagnostic clinics and cancer-detection centers because of symptoms, some of which are surely related to the gastrointestinal tract. This may account for the higher incidence in some series,‡ but we were surprised to find our incidence closely comparable to that in other large series § and appreciably higher than in some.‖

The frequency of polyps in our material is undoubtedly lower than the true incidence for two reasons. First, some patients had been proctosigmoidoscoped and had polyps removed at other clinics prior to examination here. Secondly, we unquestionably missed an appreciable number of small

* References 5 and 16.
† References 4, 11, and 12.
‡ References 6, 7, and 12.
§ References 11 and 14.
‖ References 3 and 4.

polyps. When located on the cephalad side of valves or at angulations they are quite easily missed. Each of us has had the experience of referring patients in whom we found polyps to proctologists who were unable to find them, even though we had attempted to describe the location carefully. On subsequent annual examinations we could again demonstrate them (*vide infra*). If these skilled specialists sometimes have difficulty in finding polyps, our detection rate is surely considerably less than perfect.

A study of Table 1 may shed some light on the rate of development of polyps in the age group of our patients. After the second annual examination there is an almost constant find of slightly over 2% per year. If we assume that the higher yield on the second examination results from missed lesions on the first, then it appears that men of this age group develop polyps of the rectum and sigmoid at a rate of about 2% per year. A larger number of repeat examinations will be necessary to establish this.

The Neoplastic Nature of Rectal and Colonic Polyps

Now let us examine the proposition that it is desirable to find and remove these little growths which occur with such frequency in the rectum and sigmoid.

Certainly no one can question the desirability of detecting and removing the eight (5%) polyps which were proved to contain invasive carcinoma. We believe that all will further agree that it is important to remove the eight (5%) which contained carcinoma in situ or atypism and the one carcinoid. If microscopic reports on all polyps were available, the number of malignancies would probably have been even higher. Although insufficient time has elapsed to be sure, it seems likely that all 17 (10.5%) of the polyps containing invasive carcinoma, carcinoma in situ, or carcinoid were discovered early enough to be completely eradicated, 16 of them by local excision. Finally, few will disagree concerning the desirability of detecting the three unsuspected cases of multiple polyposis. Thus the value of routine proctosigmoidoscopy in these 20 patients is established beyond reasonable doubt.

It should be emphasized that when a polyp is found, there is no way to establish its benign or malignant nature except by microscopic study. The size may bear some relation to the possibility of malignancy, but this cannot be relied upon. Invasive carcinoma has been found in a sessile polyp of only 2.5 mm. which appeared entirely benign.[17] This uncertainty as to the true nature of these neoplasms is in itself sufficient reason to remove all polyps when found.

Though formerly moot, the case for the detection and removal of benign adenomas, as a preventive measure, has been solidly built during the past two decades, despite an occasional dissenter.[3] Most experienced students of the subject presently agree that adenomatous large bowel polyps are premalignant.¶ Evidence for this has been amassed by several approaches.

Direct evidence consists of painstaking histologic studies which have demonstrated a transformation from benign adenomas to adenocarcinomas.# Collateral evidence is found in the similarity of age incidence of patients with adenomas and carcinomas, the parallel sites of predilection of polyps and cancers, and in the frequent association of polyps with cancer in resected segments of bowel. A recent study of polyps in a kindred with a very high incidence of colon cancer has contributed additional valuable proof of the relationship.[26]

The more experienced the students of the subject, the more positive are their statements concerning the evolution of adenomas into adenocarcinomas. Bacon and Broad state, "We believe that intestinal adenomas are to be considered as premalignant lesions and should be treated by destruction or removal in all instances."[20] Swinton and Warren state, "We believe that a high percentage of malignancies in the rectum and colon

¶ References 4, 5, 9, 11-15, and 18-32.

References 19, 21, and 30.

arise from previously benign polypoid tumors."[21] Rankin and Conger believe, "Most carcinomas of the large bowel originate in polyps or have polyps as their earliest manifestations."[25] Buie is convinced that "All polyps of the colon are carcinomas or will become carcinomas if they are not destroyed and if the patient lives long enough."[24] Welch and co-workers consider benign polyps "A warning signal of other present or future polyps and carcinoma of the rectum and colon."[30]

Benign adenomas have been observed to undergo malignant change in patients who have refused to have polyps removed.[24] To this latter type of evidence we can add another case.

Report of Case

The patient, who is now 63 years old, has had seven annual physical examinations at this clinic. On his fifth visit a small (8.0 mm.) polyp was found at a depth of 15 cm. on the left lateral wall. It was smooth and appeared grossly benign. Removal was advised. However, the proctologist whom he consulted was unable to locate the polyp. On his sixth admission it was again visualized and appeared unchanged. Immediate removal was again urged. Unfortunately, the lesion again eluded the proctologist. On his seventh admission the polyp remained unchanged in appearance. After the last examination the proctologist located and removed it. By this time invasive carcinoma extended to the line of dissection (Fig. 7). The base was fulgurated and there has been no recurrence to date.

Fig. 7.—Invasive carcinoma developing in a polyp which was not removed until more than two years following discovery.

Methods of Polyp Detection

There are three methods by which polyps of the rectum and sigmoid may be detected, but one is by far the most effective. Digital examination and barium-enema studies will demonstrate a small percentage, but only proctosigmoidoscopy can be relied upon.

Bargen has stated that the average physician examines the rectum with his finger to a depth of about 6 cm. The skilled examiner with maximum effort can usually examine it to about 10 cm. However, he further states that even within this distance small polyps can rarely be felt.* They blend too easily into the mucosa and cannot be distinguished from mucosal folds and feces. In our series only 40 polyps, one-fourth of the total, were within 10 cm. of the anal margin; only 4 were actually felt! If the finger can detect only the very low and comparatively large polyps, it is apparent that, as an instrument for examination of this area, it is too little and too late.

The barium enema is likewise inefficient in the rectum and low sigmoid. The multiple loops of sigmoid, the inaccessibility to palpation during fluoroscopy, and the very capaciousness of the barium-filled rectum usually obscure small polyps. We infrequently see on our films the small polyps we have found with the proctosigmoidoscope.

When polyps of the rectum and sigmoid are found, the obligation of polyp detection is not discharged. Double-contrast barium-enema examination revealed neoplasms at a higher level in one in seven in our series (Table 2). The actual number may be higher, since some of the "probables" may be confirmed. Obviously all patients with

* Bargen, J. A.: Personal communication to the authors.

TABLE 2.—*Incidence of Neoplasms Above Reach of Sigmoidoscope in Patients with Polyps Discovered by Proctosigmoidscopy*

	No. of Patients (%)
Double-contrast barium-enema studies	110
Definite polyps	14 (12.7)
Probable polyps	6 (5.4)
Annular carcinoma	1 (0.9)
Multiple polyposis	3 (2.7)

rectal and sigmoidal polyps deserve follow-through double-contrast barium-enema studies.

The Case for "Routine" Proctosigmoidoscopy

We have shown that the commonest site of neoplasms in the adult male can be adequately examined only by proctosigmoidoscopy. Others have shown that polyps are unlikely to bleed appreciably until they are about 1 cm. in size.[28] By this time 40% show malignant changes. In our series only 17 (10.5%) patients were aware of rectal bleeding. We cannot, therefore, wait for gross bleeding to prod us to examine this area properly.

When compared with other "routine" procedures in the same group of patients, proctosigmoidoscopy detected more potentially serious and yet correctible disease than any other technique. Annual routine posteroanterior and lateral chest films revealed only 119 patients with pulmonary abnormalities of any significance; a complete hemogram discovered blood disorders of all types in an approximately equal number.

In routine sigmoidoscopy we have a unique opportunity to detect early cancer and precancerous neoplasms. Adenomatous rectal polyps can be compared to little time bombs, ticking silently for months or years. They are easily accessible to direct inspection and local removal. It is the obligation of the physician to protect his patient by making this procedure a part of the physical examination.

Conclusions

1. Polyps of the rectum and sigmoid are common in adult males (6.7% in this series).

2. Approximately 5% contain invasive carcinoma, and at least an additional 5% contain carcinoma in situ or atypism.

3. Benign adenomatous polyps are potentially malignant.

4. The only satisfactory technique for detecting small polyps of this area is proctosigmoidoscopy. Digital examination is inadequate.

5. Proctosigmoidoscopy will detect more potentially serious but correctible disease than most routine procedures.

6. One in seven patients with rectal and sigmoidal polyps will have neoplasms at a higher level in the colon.

7. Double-contrast barium-enema studies should be performed on every patient with polyps of the rectum and sigmoid.

8. Polyp detection is frequently cancer detection and more frequently cancer prevention.

9. Proctosigmoidoscopy should be a part of every general examination of adults which makes a pretense of completeness.

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Subacute Thyroiditis

Report of Three Cases Treated with Cortisone

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Although first described as a clinical entity in 1904,[1] subacute thyroiditis has remained virtually unknown to most physicians. Only recently has there been an upsurge of interest in the inflammatory conditions of the thyroid gland. Whereas Cecil's "Textbook of Medicine," seventh edition (1947),[2] barely mentions it among acute thyroid conditions, the ninth edition (1955) devotes an entire column to it.

The clinical and histological picture was clearly described in 1904 by de Quervain, who collected cases from the literature going back almost 100 years. He distinguished primary nonsuppurative thyroiditis from secondary thyroiditis occurring in a variety of infectious diseases, such as typhoid and malaria. In 1936 he added 8 cases and collected 62 more from the literature.[3]

There are several names for this disease, such as, de Quervain's thyroiditis, acute recurrent, pseudotuberculous, and giant-cell thyroiditis. It is nowadays usually designated as subacute thyroiditis.[4] This term distinguishes subacute thyroiditis from the suppurative and nonsuppurative forms which last only a few days, and the chronic forms, Hashimoto's and Riedel's struma, to which they are not related.

I have had occasion to observe and treat three patients with subacute thyroiditis, using cortisone, and one patient with carcinoma of the thyroid which closely mimicked thyroiditis.

Report of Cases

CASE 1.—A 41-year-old Jewish refugee housewife was first seen by me on Sept. 3, 1953. Her symptoms had appeared five weeks before, while she was on vacation in upstate New York, with severe pain at the base of the throat radiating to the left side of the neck, head, and ear. At the same time she had developed a short dry cough. Three weeks later she developed fever rising from 100 F in the morning to 102 F in the afternoon. She was treated with penicillin and oxytetracyline (Terramycin), but, when after two weeks the fever remained unchanged, she returned to New York City, where she consulted an otolaryngologist who referred her to me.

Her past history consisted of nervousness going back many years with many somatic complaints as well as a history of "stomach ulcer" and "rheumatism."

On physical examination the patient did not appear ill in spite of a temperature of 101.4 F (oral). The significant findings consisted of a symmetrically enlarged thyroid gland, firm and exquisitely tender. She had tachycardia and some small glands in the axillae which may or may not have any significance. There was a Grade 1 apical murmur, probably functional. The pharynx was slightly injected. The hemoglobin was 13 gm. per 100 cc.; white blood cell count 9200; polymorphonuclears, 78; lymphocytes, 22.

The patient was admitted to the Beth-El Hospital on Sept. 4, 1955. She was given propylthiuracil, 150 mg. a day. Therapy continued from Sept. 4 to Sept. 16, 1953, during which time there was no change in fever or symptoms. The white blood cell count and blood chemistries were normal. Blood cholesterol was 242 mg. per 100 cc. Chest x-ray, electrocardiogram, and gastrointestinal series were all normal.

Sedimentation rate continued high: 29, 34, 35, 46 mm. in one hour (Wintrobe). On Sept. 16 corticotropin (ACTH), 25 mg. I. V., was started daily. The response was dramatic. The temperature became normal the next day and remained normal. Subjective symptoms were markedly alleviated. On Sept. 26, corticotropin was discontinued and 200 mg. of cortisone was given. This dose was gradually reduced to 100 mg. With the administration of 100 mg. subjective symptoms recurred with no fever. The cortisone dose was raised to 150 mg. daily, which was continued after her discharge on Oct. 3, 1953.

I observed the patient from Oct. 5, 1953, to March 3, 1954. There was a marked decrease in the size and tenderness of the gland by Nov. 1, 1953, a month after discharge. The sedimentation

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rate continued to be elevated, however, 45 mm. in one hour. Cortisone was reduced to 75 mg. and later 50 mg. a day. By Dec. 14, 1953, the sedimentation rate was consistently normal—7 mm. and 10 mm. in one hour. The gland was barely palpable and not tender. The patient was completely symptom-free. The basal metabolic rate was +8. Cortisone was stopped after having been administered for three months. There was no recurrence.

Comment.—This classical case of subacute thyroiditis was initially not diagnosed, simply because the physicians did not think of this condition. It is not likely that the duration of the disease was shortened by cortisone. However, by the administration of cortisone the patient was kept symptom-free and able to continue her normal activities, whereas without this medication she may well have been invalided during this entire period. The return of symptoms on premature cessation or reduction of the dose of cortisone emphasizes the importance of continuous therapy until signs of the disease (tenderness and enlargement of the gland, elevated sedimentation rate) have disappeared.

CASE 2.—A 45-year-old man, school principal, fell ill on Aug. 20, 1953, while on vacation in New England three weeks before admission to the Beth El Hospital. Illness began with pain over the region of the thyroid, radiating to both ears and back of the head, preventing the patient from sleeping. There was no cough or pain on swallowing but marked increase of pain on extending the neck to shave and also on sneezing or clearing the throat. His shirt collar felt a little tight. The temperature was taken and found to be normal. He returned home and on Sept. 7 (one week before admission) developed fever.

He was seen on Sept. 12, 1953, and hospitalized the next day. The patient did not look ill but was very uncomfortable. Both lobes of the thyroid were enlarged, firm, and very tender. The rest of the physical examination was negative.

The basal metabolic rate was +14. The white blood cell count was 12,400 to 4500 with a normal differential, the hemoglobin normal.

The sedimentation rate was 18 mm. in one hour (Wintrobe) on admission and 24 mm. in one hour a few days later. Blood chemistries were normal except for a high cholesterol value—372 mg. per 100 cc., total; 108 mg. per 100 cc., free. Radioactive iodine uptake was 1.5%.

The patient was put on oxytetracycline therapy on admission. The temperature, which was 101.8 F on admission, came down to normal in three days, and there was a marked subjective improvement. The thyroid gland remained tender and unchanged in size.

On Sept. 21, 1953, while the patient was still on oxytetracycline therapy, there was a return of temperature to 101.8 F and a recurrence of pain in the same degree as before.

On Sept. 22 cortisone therapy was begun, 300 mg. the first day, 200 mg. the second day, and 100 mg. thereafter. In 24 hours (Sept. 23) the temperature had returned to normal, the pain had completely disappeared, and the gland was no longer tender. On Sept. 26 the gland was definitely smaller, and the patient was discharged while taking 100 mg. of cortisone daily.

Two weeks later his thyroid gland was barely palpable. He was feeling entirely well. He continued, however, to have leucocytosis: 15,000 white blood cells with 78% polymorphonuclear leucocytes, and an elevated sedimentation rate—32 mm. in one hour (microtechnique). Cortisone was reduced. A month after discharge physical examination was entirely negative. The thyroid was not palpable. White cell count and sedimentation rates were normal. Cortisone was continued in decreasing doses for another month and then stopped. Patient was observed for a year and a half after this. There was no recurrence.

Comment.—This was another fairly classical case of subacute thyroiditis. There was a brief remission, part of the natural course of the disease, which coincided with antibiotic therapy. However, symptoms and signs returned while this treatment was still being continued. The radioactive iodine uptake was extremely low, as is commonly observed in this disease.

There was an immediate response to cortisone, which was continued until the thyroid gland and sedimentation rate had returned to normal.

There was no recurrence on discontinuing cortisone therapy.

CASE 3.—A 56-year-old Jewish housewife gave a history of vague pain in the region of the thyroid since the summer. Four weeks previous to the first examination the pain became severe, radiating to the right ear and back of the head. At the same time the temperature rose to 102 F. She consulted a physician, who informed her that she had an infected thyroid and treated her with penicillin, chlortetracyline (Aureomycin), and an ice collar. The fever lasted several weeks.

A few days ago the pain recurred on the left side of the neck and head; the temperature was

100 F. There was no pain on swallowing but pain was present on coughing.

Past history was irrelevant. She had had a myomectomy 30 years ago and a hysterectomy 2 years ago.

Physical examination revealed the left lobe of the thyroid to be enlarged, firm, and tender. The right lobe, which had been involved previously, now seemed to have returned to normal. The blood pressure was 130/80; pulse was normal; hemoglobin was 12.5 gm.; sedimentation rate was 25 mm. in 20 minutes (micromethod). The urine was negative. The patient was put on cortisone therapy, 100 mg. a day.

The patient was again examined on Nov. 22, 1954 (five days after the first visit). The pain was entirely gone, and she reported feeling well. The left lobe was no longer tender.

Two weeks later the thyroid was no longer palpable, and the patient felt entirely well.

Six weeks after therapy was begun, cortisone was discontinued. There was no recurrence.

Comment.—This is a case of a so-called creeping or migrating thyroiditis in which at first only one lobe is involved and later the other lobe becomes enlarged and tender. The disease ran its usual course and the second lobe might well have returned to normal without cortisone therapy. However, with cortisone, the temperature came down to normal and all the symptoms disappeared within a few days instead of weeks or months. Cortisone was continued until thyroid enlargement disappeared. No recurrence took place on stopping it.

Case of Thyroid Carcinoma, Simulating Thyroiditis

A case of thyroid carcinoma is included here because of its clinical resemblance to thyroiditis.

The patient was a 74-year-old woman, retired nurse, without a previous history of thyroid involvement. She was admitted to the Beth El Hospital on Jan. 7, 1954, because of acute onset of pain and swelling of the thyroid gland. The pain radiated to the left ear and increased on swallowing. The patient developed a temperature of 101-102 F.

The patient was a diabetic and had had a coronary occlusion two years before. There was no previous thyroid enlargement.

The thyroid gland was enlarged to about double the normal size, hard and tender to touch. The neck circumference was 15¼ in. The basal metabolic rate was +26, and the radioactive iodine uptake was 14%.

Clinically it was thought that she had thyroiditis. Because of her diabetic and cardiac status, steroid therapy was withheld. The temperature came down spontaneously, but the pain and swelling persisted.

On Jan. 17, 1955, after some hesitation, she was given corticotropin, 30 units, intramuscularly b.i.d. This was continued until Jan. 31. There was no adverse effect on her diabetic or cardiac status. However, there was no favorable effect on her thyroid either. The patient was transferred to surgery, where on operation a carcinoma was found.

Comment.—This was a case of carcinoma of the thyroid which so closely resembled subacute thyroiditis that a clinical differentiation was, in my opinion, difficult if not impossible. A biopsy in such a case might implant carcinoma cells if the lesion is malignant, and for that reason was refused by the surgeons. The relatively normal radioactive iodine uptake gave the first clue that this was not a subacute thyroiditis, in which extremely low readings are invariably found. This was later confirmed by the patient's failure to respond to cortisone.

It is suggested that when radioactive iodine uptake is not available, steroid therapy continued for two or three days would be sufficient to differentiate the two conditions, thus avoiding unnecessary surgery or the risk of biopsy.

The use of cortisone as a therapeutic test to differentiate thyroiditis from cancer was first mentioned by Crile.[5]

General Comment

The cause of subacute thyroiditis is unknown, but it is assumed to be viral. The characteristic pathology is thought to be due to extravasation of thyroglobulin[4] (caused by inflammation and destruction of follicles) and a subsequent foreign-body reaction to it. It occurs most commonly in the fourth and fifth decade, more often in women than in men—about four or six to one.

The onset is fairly sudden, the patient sometimes remembering the exact date of onset (Case 2), but it may be more insidious (as in Case 3). The chief complaint is pain, which can precede fever by several weeks. It is located over the thyroid gland

and radiates to one or both ears. Extending the neck as in shaving makes it worse. There is often a short dry cough which increases the pain, and pain is also commonly increased by swallowing. The fever is moderate, up to 102 F, and the patient (and often the doctor) regards the episode at first as an upper respiratory infection. Twenty-five per cent of the cases are said to be preceded by an upper respiratory infection. However, it is possible that in some cases the onset of thyroiditis itself was mistakenly thought to be a respiratory infection. The diagnosis can nearly always be made on physical examination. The thyroid, usually both lobes, but sometimes only one at first, is moderately enlarged, usually not more than double the normal size, and is often not noticed by the patient. The gland is very firm (though not stony hard), extremely tender, and moves on swallowing. An enlarged soft gland with redness of overlying skin has been mentioned.[6] This, however, is unusual.

There is tachycardia, out of proportion to the temperature. The patient does not usually look very sick. He (or she) may be nervous and give the impression of hyperthyroidism. The basal metabolic rate is often slightly elevated but not much out of proportion to the temperature. The protein-bound iodine is often elevated at first (probably due to the spill of thyroglobulin into the blood stream), but may be normal.* Radioactive iodine uptake levels are always, and characteristically, very low (in myxedema range)—about 5% or even less.†

The white cell count is often slightly elevated but is variable. Crile even denies that it is ever elevated.[11] A high sedimentation rate, however, is almost invariably present and parallels the course of the disease. Although minimized by some,[12] it is held to be a helpful sign by almost all observers.

The course is benign, the patient eventually retaining a perfectly normal gland in size and function in almost all cases. Rarely myxedema has been reported.‡ However, the disease can last several months, causing a good deal of pain and disability. The course is, furthermore, very variable and subject to spontaneous remissions and exacerbations. This makes evaluation of therapy rather treacherous.

As in any variable and self-limited disease, success has been claimed for a wide variety of treatments.

Surgical excision, although once advocated for stubborn cases, is no longer used. The same holds true of the surgical transection of the isthmus of the gland. Penicillin and other antibiotics have been widely used. It is now generally held that they are useless.

Bed rest, cold or warm compresses, and analgesics were widely used before the introduction of specific measures. Some still believe that strict bed rest for several weeks is the best form of treatment.[12]

X-ray therapy is the oldest effective modality. (It was mentioned by de Quervain.[3] Two hundred roentgen units given three or four or at most five times is the usual recommended dose. Excellent results have been recorded by reliable observers.§ However, its effectiveness has been challenged by some.‖ Also, permanent hypothyroidism has been reported. This is a serious objection in the treatment of a benign disease.

Thiouracil was first introduced by King, in 1945.[15] Favorable reports have followed the use of propylthiuracil,[7] but failures have likewise been reported.[12]

The newest and increasingly popular method is cortisone or corticotropin.¶ It was apparently first used by Dr. Wineblad in Denmark and was first used in this country by Crile. The mode of action is no doubt by suppressing the tissue reaction to the noxious agent, whatever it may happen to be. The course of the disease is probably not shortened, but the patient can be kept

* References 6, 7, and 8.
† References 8, 9, and 10.
‡ References 2, 7, and 10.
§ References 4, 11, 13, and 14.
‖ References 12 and 15.
¶ References 5, 6, 16, 17, 18, 19, 20, 21, and 22.

symptom-free and at his or her normal work while the disease is running its course. The self-limited nature of the disease, not usually exceeding a few months, makes it very suitable for this type of therapy. If cortisone is stopped or reduced below an effective level prematurely, symptoms and signs come back. They can again be suppressed by increasing the dose. After the first few days on 300 to 200 mg. the patient has his dose reduced slowly to the minimum level that will control symptoms. It is discontinued when the disease seems to be cured, as evidenced by the return of the gland to normal size and a normal sedimentation rate.

The effect of steroid therapy is dramatic, with marked subjective and objective improvement within 24 hours. Only one real failure has been reported.[24] In another alleged case [25] the patient had suppuration of the thyroid but no subacute thyroiditis. In another patient [26] the disease responded dramatically to cortisone, but symptoms and signs returned when this medication was discontinued two weeks later. Most early workers who used cortisone in subacute thyroiditis continued it for only a week or two; it is remarkable that they had as much success as they did. Crile stressed the fact that, although the immediate response was always dramatic, relapses were common. He advocated following cortisone with x-ray therapy. Werner likewise supplemented cortisone with x-ray in one case.[28]

In my opinion this is not necessary. One should simply continue to administer cortisone until the disease has run its course.

Conclusions

1. Subacute thyroiditis is not rare and is likely to be encountered in the course of the practice of medicine.

2. It has fairly characteristic signs and symptoms and can be readily diagnosed at the bedside if thought of.

3. The course is almost always benign, the thyroid returning to normal size and function after a variable interval without treatment.

4. It is most effectively treated by cortisone, which should be continued until the disease has run its course as shown by normal sedimentation rate and return of the gland to normal size.

5. In rare cases, it may be confused with carcinoma of the thyroid. It is suggested that the two conditions can be differentiated by the result of the administration of cortisone for two or three days. A very low radioactive iodine uptake is also a characteristic sign of subacute thyroiditis. Needless to say, this diagnostic method is not always available to the practitioner.

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Cerebral Blood Flow in Polycythemia Vera

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Polycythemia vera is a disease of unknown etiology characterized by an abnormally increased red cell mass. Its symptoms and complications are due to plethora and to thrombotic and hemorrhagic phenomena within various organs. Thrombosis is attributed to the high platelet count and to circulatory stagnation due to increased blood viscosity. This report is concerned with cerebral hemodynamics and their alteration by treatment during the several stages of the disease.

Report of Case

A 48-year-old Negro woman entered the District of Columbia General Hospital on Dec. 20, 1954, with the chief complaint of "spitting up blood." One month prior to admission the patient had suddenly become aware of a sensation of fullness in her mouth and expectorated "about a pint" of bright red blood. In the course of a similar, second episode, one week prior to admission, she had brought up "about one cupful." Two weeks prior to admission she had experienced chills and fever for one day. There was no history of chest pain, cough, dyspnea, or thrombotic venous disease of the legs. For the preceding two years the patient had noted a significant decrease in vigor and strength and had felt "sick" and "run down." There had been a 30 lb. weight loss, from 150 to 120 lb. in the seven months prior to admission. There were no specific complaints or pertinent information in her past medical history, family history, social history, or review of systems.

Physical examination revealed a well-developed, moderately well-nourished Negro woman, in no distress. The oral temperature was 99 F, pulse 80 per minute, and blood pressure 240/140 mm. of Hg. The conjunctivae, buccal mucosa, nailbeds, and palms were of a suffused and dusky appearance. The ocular fundi showed only mild diminution in the A:V ratio, with no venous engorgement noted. The lungs were clear. The heart was moderately enlarged, with a Grade 2 systolic blowing murmur over the precordium; A_2 was louder than P_2 and of tambour quality. The liver edge was barely palpable, and the spleen was palpable only on deep inspiration. The pelvic and neurological examinations were negative.

The admission hemogram disclosed a leucocyte count of 5500, a hemoglobin concentration of 19 gm per 100 cc., and a hematocrit of 68%. These findings initiated a detailed hemotologic investigation which confirmed the diagnosis of polycythemia vera. The details are presented in Table 1.

TABLE 1.—*Laboratory Data of Patient with Polycythemia Vera*

Hematocrit	68; 64; 65; 69
Hemoglobin	19.0; 20.5 gm./100 cc.
Red cell count	5.35; 6.68; 6.61 million
White cell count	5,500; 11,400; 12,700
Differential	Neutrophiles, 76%; lymphocytes, 18%; monocytes, 2%; eosinophiles, 2%
Platelets	496,000; 804,000; 694,000
Reticulocytes	1.1%; 1.4%
Blood volume (iodinated albumin method)	Total blood vol., 5,148 cc. (95 cc./kg.) RBC mass, 3,552 cc. (65 cc./kg.) Plasma volume, 1,596 cc. (29 cc./kg.)
Bone marrow	"Hyperplastic marrow with marked increase in all normal marrow elements with a relative increase in rubricytes."
Uric acid	4.4 mg./100 cc.
Circulation time	Arm-tongue (dehydrocholic acid [decholin]), 34 sec. Arm-lung (ether), 15 sec.
Arterial O_2 saturation (at rest; room air)	97%

Chest x-ray on admission disclosed moderate cardiomegaly and a soft infiltration in the third and fourth right anterior interspaces. Reexamination, on Jan. 11, 1955, disclosed complete clearing of the infiltration, a radiological response considered consistent with pulmonary infarction. Bronchoscopy was negative, as were cultures of

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bronchial washings and sputum specimens for acid-fast organisms. Pulmonary function studies* were interpreted as "failing to reveal a shunt mechanism responsible for the polycythemia."

Cerebral hemodynamic and metabolic studies were performed twice, for control values when the hematocrit was 69% and 63% and also after repeated venesection had reduced the hematocrit to 51%. Scheinberg and Stead's modification[1] of the Kety and Schmidt procedure[2] for the determination of cerebral blood flow (CBF) was applied in this study. The gas mixtures utilized were those described by Kety.[3] Blood oxygen was determined by the manometric technique of Van Slyke and Neill.[4] Mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer.[4]

The patient was asymptomatic and ambulatory during her early hospital stay, and following the establishment of the diagnosis of polycythemia vera, she was given a course of radiophosphorus (P^{32}), 0.1 mc. per kilogram of body weight, in two divided oral doses. On the day immediately prior to her planned discharge, the patient suddenly developed a left hemiparesis and over the next several days suffered several additional episodes of cerebral vascular occlusion. The neurological findings disclosed right-sided deficits of cranial nerves 5, 7, 9, and 10, with marked right-sided and moderate left-sided paresis, indicating a pseudobulbar palsy due to repeated or progressive thromboses. In an attempt to prevent further cerebral thromboses, venesection was repeatedly performed until the hematocrit reached 51%. This required a total withdrawal of 3000 cc. of blood over a 13-day period. In spite of supportive therapy, the patient died after a hospital course of 102 days.

* Performed by Dr. Georges McCormick.

At necropsy, the principal findings were encephalomalacia due to multiple cerebral infarcts, several recent pulmonary emboli with infarction (no definite evidence of old pulmonary infarction corresponding to the initial presenting episode of hemoptysis could be detected), and an old myocardial infarction. The bone marrow showed an increase in all cellular elements.

Comment

The diagnosis of polycythemia vera seems to have been established by virtue of the pertinent clinical and laboratory features presented. The patient had no clinical (or autopsy) evidence of intracardiac or intrapulmonary shunt or of functionally significant parenchymal lung disease and no history of high-altitude residence.

The cerebral hemodynamic and metabolic findings are presented in Table 2. The cerebral vascular resistance was persistently elevated in the period before phlebotomy. This elevation was considered not to be due entirely to the increased vasomotor tone characterizing the hypertensive state, since in nonpolycythemic hypertensives the cerebral vascular resistance is much lower.[5] The decrease in cerebral vascular resistance following phlebotomy supports this belief, since the procedure induces a reduction of the abnormally high blood viscosity. The cerebral metabolic rate prior to the thrombotic episodes was normal. Although the cerebral blood flow was markedly reduced,

TABLE 2.—*Cerebral Blood Flow Studies of Patient with Polycythemia Vera**

	MAP	Hct	CVR	CBF	$CMRO_2$	AO_2	VO_2	$(A\text{-}V)O_2$	Comment
Normal values	100	45	1.7	55.5	3.5	19.00	12.00	7.00	
Case									
Jan. 13	155	69	5.7	27.2	3.5	23.56	12.16	11.40	No cerebral complications
Jan. 25	128	63	4.9	26.3	3.1	22.51	10.72	11.79	Left hemiparesis
	134	63	3.3	40.1	3.1	22.96	15.03	7.68	5% CO_2 inhalation
Feb. 8	124	52	2.0	62.2	2.4	17.38	13.45	3.93	Multiple cerebral thrombi; stupor

* MAP signifies mean arterial blood pressure in mm. of Hg; Hct., hematocrit in per cent; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain; CBF, cerebral blood flow in cc./min./100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 gm. of brain; AO_2, arterial oxygen in vol.%; VO_2, venous oxygen in vol.%; and $(A\text{-}V)O_2$, arteriovenous oxygen difference in vol.%.

this was compensated for by an increased utilization of oxygen per unit of blood. (The lowest cerebral blood flow rate recorded in Kety's [6] experience—22 cc/100 gm/min.—was in a case of polycythemia vera.) Since the oxygen-binding capacity per unit of blood is so high, this involves no diminution in oxygen content of venous blood to subnormal levels.

The inhalation of 5% CO_2 had the characteristic effect observed in nonpolycythemics † of dilating the cerebral vessels. As a result, the cerebral vascular resistance decreased, the cerebral blood flow rate increased, and the arteriovenous oxygen difference decreased; the cerebral metabolic rate (oxygen consumption) remained unchanged. These findings are at variance with the conclusion of Gadermann [9] (who, however, appears to refer to the body circulation as a whole) that there is in polycythemia vera a "lack of stretching ability of the vessels as a result of increased blood volume."

Measurements performed following numerous cerebral thrombotic episodes and a lowering of the hematocrit disclose a change to values approximating normal for cerebral vascular resistance and cerebral blood flow, with a moderate decrease in cerebral metabolic rate (oxygen consumption) ($CMRO_2$). These indicate that although cerebral tissue was being freely perfused, metabolic work was not being done in normal amounts by injured and therefore malfunctioning tissue.

This case illustrates the ever-present threat of vascular thrombosis in polycythemia vera. It is common practice first to reduce the hematocrit by the most rapid and direct means available (repeated phlebotomy) while at the same time instituting more slowly acting maintenance therapy, such as acetylphenylhydrazine or radiophosphorus (P^{32}). In the interim between the initiation of the diagnostic work-up in a case of suspected polycythemia vera and the achievement by means of phlebotomy of a relatively safe hematocrit level, the frequent daily use of CO_2 inhalation seems to be a reasonable, although untried, prophylactic measure as well as a therapeutic one in the event of cerebral thrombosis.

In a disease characterized by thrombotic phenomena, the therapeutic consideration of anticoagulant therapy naturally arises. In polycythemia vera, however, a simultaneous hemorrhagic tendency exists which has been attributed both to the plethora of blood in the tissues and to poor clot retraction. Although we are unaware of a well-controlled study utilizing anticoagulants, we feel that in view of the potential dangers of its use and the complete safety and sound physiological basis for the use of CO_2, the latter might well deserve prior consideration as a prophylactic agent.

Summary

A case of polycythemia vera is presented in which cerebral blood flow studies were performed.

Additional conclusions regarding cerebral hemodynamics in polycythemia are derived.

Therapeutic application of CO_2 inhalation (in conjunction with conventional therapy) is suggested as of possible value in the prophylaxis and therapy of cerebral vascular occulusion in polycythemia vera.

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Treatment in Internal Medicine

MANAGEMENT OF RHEUMATOID ARTHRITIS

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MOST CURRENT reports on rheumatic diseases deal with treatment; many compare the effects of particular pharmaceutical agents. Properly regarded as fragments of clinical investigation, such reports do not mean that the successful management of rheumatoid arthritis depends on the administration of one or the other medicine. To be sure, several drugs have definite, more or less circumscribed usefulness. Some rheumatoid patients treated with a new preparation may also have been substantially improved at some time. But if one in practice were to rely foremost on his selection of antirheumatic drugs, he would oftener than not make merely a choice of embarrassments.

Rationale

There is as yet no remedy which can be counted upon to arrest rheumatoid arthritis. None has induced remissions as consistently as have either pregnancy or jaundice. But even though Factor X, credited by Hench with reversibility of rheumatoid arthritis, remains unknown, the disease also commonly abates under other, less distinctive circumstances. Retrospective analysis has demonstrated the intercurrence of single or several remissions in 27% of 293 chronic cases (Short, Reynolds, Bauer, and Beauregard). For no obvious reason, interludes free from arthritis happen and may last for years and even decades. Such considerations do not furnish a guide to individual prognosis in rheumatoid arthritis, but they do indicate a natural trend not invariably grave.

To date it has not been statistically proved that nonspecific treatment, i.e., comprehensive management, modifies the course of rheumatoid arthritis. There is, however, clinical experience suggesting that it does do so. Short and Bauer observed 250 patients treated by simple medical and orthopedic measures, and found about one-half improved after 10 years, whereas slightly over one-third had deteriorated. Of patients who came to treatment within the first six months of their illness, 81% had improved. Duthie reported that of 282 patients similarly treated, 60% gained in functional capacity, and the disease became inactive in 20% of the total number. Jellinek found that a complete remission or major improvement (Grades I and II) occurred in 50, or 75%, of 68 patients in all stages who had been previously unresponsive and partially disabled and who were treated at Lakeville Sanatorium with nonspecific and corrective measures for an average time of five months. Functional competence (Class I and II) was attained by 37% of incapacitated patients (Class III and IV) in the advanced stages of the disease.

The rationale for comprehensive management of rheumatoid arthritis thus issues from the failure of any single therapeutic agent and from the likely assumption that supportive, preventive, and corrective measures beneficially influence the virulence of and the impairments due to the disease.

Indications

The typical hazard of rheumatoid disease derives from the chronic presence of inflammation in connective tissue.

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Occasionally, the pathological process remains localized to some joints or even to one joint, or to a part of an anatomic system, like lymph nodes, blood vessels, or pleura. Limited and shifting foci may recur intermittently for years, whereas in other cases the disease is disseminated at once and for long periods throughout the connective tissue of several systems and organs. Impairment of specialized cells and reactive fibrosis, the results of chronic inflammation, therefore become the dual risk to connective tissue proper and to structures which connective tissue helps to constitute. Hence, in all active cases, management has the twofold aim of suppressing the primary inflammatory process and of counteracting cicatrization or its effects. The therapeutic objectives in rheumatoid disease tend to be movable and multiple. They call for measures adapted to phase, intensity, extent, and sequellae of the ailment and to the variables of humans concerned with it.

One group of patients will have had, perhaps for months, suggestive but undiagnosable manifestations, such as fatigue, weight loss, vasomotor disturbances, paresthesias, or periarticular stiffness. When the diagnosis remains doubtful, it is best to proceed as though it were established and to treat the suspect by regulation of general hygiene and by reduction of occupational or other usual duties. It may be advisable to curtail all stressful activities by one-third to one-half or to prescribe a full vacation for two to four weeks. Unless otherwise indicated, no medicine should be given except, possibly, a general vitamin preparation. The patient should be checked again within a month if no more definite symptoms appear sooner.

In other patients the presence of synovitis, monarticular or multiple, particularly in symmetrical distribution, may permit a more definite diagnosis. Under these circumstances the same regimen should be instituted, and it will then also be necessary to prescribe salicylates on a regular schedule. These patients should have physical therapy to any joints which are even mildly involved on detailed examination. Elbows and shoulders are especially prone to early and silent loss of range. At this stage one should prescribe a firm mattress, firm and low support for the neck, and proper positioning of individually affected joints at nighttime and during stated periods of rest. Inflamed articulations should be guarded from strain. A program of this kind may be continued with weekly checks for three to six months. During this time, also, any precipitating factors discovered in association with the onset or a recurrence should, if possible, be treated. If the disease comes under gradual control, the patient may attempt to resume his usual activities, but he should be protected from ordinary exertion for three months after he has become completly asymptomatic. If the condition deteriorates despite these measures, the practitioner should then suggest a regimen of greater restriction, preferably in a chronic disease hospital where patients may receive comprehensive supportive care and systematic physical therapy. At present, sanatoria are not sufficiently available, so that it will usually be necessary to make comparable arrangements at the patient's home.

Assuming the physician takes charge of a patient who has had persistently active rheumatoid arthritis for many months, equally careful evaluation should be made. Patients at this stage, indeed, require more initial attention and orientation, as they are likely to have started their treatment on an inauspicious program. Additional effort will be needed to reestablish their confidence in themselves and in their physician. He may then choose to suggest a brief period of study in a general hospital. This will be particularly useful where one needs to determine accurately the degree of critical damage to joints, so as

to differentiate it from reversible limitations due to functional demands on impaired articulations. Patients at this stage may require joint aspiration, biopsies, or tests for precipitating factors, and they may be in need of orthopedic measures, such as splinting, traction, or manipulation. Many patients in this group will have been previously treated with drugs whose withdrawal can be more readily effected under hospital conditions. A further advantage of two or three weeks' hospitalization at this stage is the schooling of the patient in the program to be initiated, especially of physical therapy. From various observations, including the clinical response, the practitioner will then be able to decide whether an ambulatory regimen or home care or sanatorium treatment are indicated. Tenaciously active and diffuse rheumatoid disease should be considered an indication for comprehensive institutional treatment. Where chronic disease hospitals are not available, one must attempt to substitute a facsimile elsewhere. No matter how troublesome these alternatives may be, the difficulties will eventually be compounded if one uses drug therapy instead of rational management.

For cases of protracted, subacute rheumatoid arthritis with little or no constitutional disease, whose effect is limited to a few joints, the practitioner may continue with ambulatory treatment. In such cases, again, general activity should be reduced; salicylates, physical therapy, and dietary supplements comprising the chief elements of a supportive program should be prescribed; and orthopedic supports should be provided for the affected joints. Such patients may be considered for intra-articular injection of corticosteroids every two to four weeks, as necessary. As an alternative adjunct to treatment of ambulatory patients with polyarticular involvement, the physician may choose chrysotherapy.

In still another group, the disease will be so far advanced that extensive destruction and/or ankyloses have occurred, and the patients will have sustained a marked functional deficit. In some the rheumatoid process will be progressively active. Then the practitioner may prefer to consult with specialists in orthopedic surgery and rehabilitation. The management of such patients is usually too complex for any individual physician and requires multiple technical facilities for restorative procedures (Lowman, Lee, and Rusk). One should envisage hospital care for at least six months; and if it proves unsuccessful, arrangements for custodial maintenance should be made, where patients can be reevaluated every two to three months. Other rheumatoid patients with chronic and advanced disease will have suffered impairment of only a few articulations, but severe enough to preclude normal living. These patients can frequently be restored to useful occupations, modified to their handicap. They also, as a rule, require comprehensive rehabilitative work for a period of six months to a year in a diversely equipped center. A third group of patients with multiple deformities no longer have active disease; but marked residual crippling present for a number of years may have forced them into acceptance of and adjustment to their limitations. One should not lightly undertake to disturb this equilibrium for the uncertain prospect of partial rehabilitation after months or years of painful, costly effort. Prior to the institution of any extensive program of restoration, one should assay the crippled patient's physical, emotional, and intellectual resources.

Methods

When a physician accepts the responsibility of caring for a rheumatoid patient and has completed his clinical evaluation, he may profitably spend an appointed half hour in discussing his aims and methods with the patient and perhaps with some members of the patient's family. It will spare time and disappointment if doctor and patient reach an understanding of the opportunities and risks inherent in the course of this chronic ailment.

Neither should assume that the outlook is inexorably hopeless, neither should expect or rely on a medicinal cure, and both must be prepared to work for therapeutic goals short of perfection. The physician member of this team will principally be a medical teacher by whose instruction and guidance the arthritic learns to help himself.

Relaxation.—Irrespective of etiologic theories, the moderation of stress has a solid empirical reputation in the management of rheumatoid arthritis. Therapeutic rest may at times be achieved by reducing unessential expenditures of physical and emotional energy. But the curtailment of overtly excessive or average activities may not leave a positive balance of strength when there are concealed drains on somatic and psychologic vitality. While relative restraint in daily exertion is indicated for any patient with diffuse rheumatoid inflammation, he should not be made inactive and dependent. Relaxation will often be furthered by directed occupational therapy. Whether or not patients have specific emotional disturbances, therapeutic rest should provide them with opportunities for diversional and constructive occupation. The precise relation between hours of bedrest, of sitting up, and of exercising will vary with the degree and form of rheumatoid involvement. All moderately severe cases should have nocturnal rest for no less than 10 hours, and 2 to 4 additional hours of each day should be spent in recumbency at intervals. In severe cases, physical exertion should be limited to planned therapy and bathroom privileges. There is no general rule for the prescription of sedatives and relaxing drugs.

Salicylates.—Acetylsalicylic acid and related compounds have several practical functions. They are effective analgesics for rheumatic pain, they reduce muscle spasm, and they have as yet not fully defined and perhaps centrally mediated anti-inflammatory action. The choice among various preparations will depend on a number of incidentals, such as the patient's tolerance. Commonly available preparations are pharmaceutically equivalent in comparable amounts. It is good practice to specify 3 to 8 gm. of acetylsalicylic acid daily, at regular, stated intervals, for instance, 0.6 gm. upon awakening and every three hours. The dosage may be adjusted, but variations should usually not be made oftener than every two weeks and should not be left to the patient's discretion. However, tinnitus and loss of hearing require immediate reduction of the dose. Gastric irritation can frequently be avoided or minimized by taking salicylates with food or in a coated or a buffered preparation. Rectal suppositories containing 1 to 2 gm. of salicylates in coconut fat may be used at bedtime or for stated periods of rest. In some patients who appear not to respond to acetylsalicylic acid, the salicylate level of the blood (less than 20 mg. per 100 cc.) may prove the dose inadequate. The combination of salicylates with organic compounds has no proved practical advantage. Some patients, allergic to salicylates, may be able to tolerate sodium gentisate, which has equivalent antirheumatic effects. Opiates are contraindicated, except for subordinate or separate purposes.

Precipitating Factors.—In approximately half the cases, the onset or a flare-up are temporally associated with one or more so-called contributing circumstances. Prominent in this pattern are injuries, including physical strains and operations; infections due to a wide variety of pathogens, bacterial and viral, or even immunization to such; emotional disturbances; and endocrine crises, including puberty, pregnancy, and menopause. We have no proof that treatment of these precipitating factors, though they be clearly discernible and amenable to therapy in some cases, modifies the immediate course or ultimate outcome of rheumatoid arthritis. The management of associated disturbances is merely a dictate of general hygiene, and the practitioner should make efforts both to identify and to control them according to the requirements of meticulous medical care.

Physical strains due to occupational or diversional overexertion can frequently be reduced. One should attend to overt infections and conservatively search for and treat foci in the oropharynx and in the pulmonary, intestinal, and urinary tracts. Operative procedures undertaken during the course of active rheumatoid disease in a potentially septic field require the prophylactic use of such antibiotics as may be efficacious. Psychological maladjustments are common in the course of chronic illness, but it seems likely that emotional tensions, both chronic and fulminating, primarily influence the development of rheumatoid disease in some cases. One cannot yet define the role of psychiatric care in rheumatoid arthritis, and it is probable that emotional disturbances do not always participate in the pathogenesis. However, practitioners should be alert to the possibility that psychotherapy may be indicated beyond the need of a chronically ill patient for reassurance. The predilection of typical rheumatoid arthritis for women and the association of onset with various phases of the sexual cycle are notorious. Nongonadal endocrinopathies, such as Graves' disease and Addison's disease, can also precipitate arthritis. Recent studies concerned with adrenocortical hormones and pituitary and hypothalamic secretions have widened the scope of endocrines possibly concerned with rheumatoid disease. It is not likely that a specific lack or excess of any one hormone is the cause of rheumatoid arthritis. There is no evidence that compensation for definitely deficient factors ameliorates the course of the disease. Correction of any overt disorders of the endocrine system will only serve to improve the rheumatoid patient's

general health. In clinical practice, most patients show the concurrence of several precipitating factors with the development of arthritis, and there is at present no reason to stress the management of one over the other.

Diet.—No single element or category of food can be credited with etiologic or curative significance. Yet dietary management must be an important part of the medical care for patients, the majority of whom are undernourished and underweight. For such cases, usually with virulent disease, the caloric intake of a normally proportioned diet should be raised, and to patients who have experienced severe wasting of tissues, supplements of protein hydrolysate should be given. Since many active cases are deficient in several vitamins, a multiple vitamin preparation in therapeutic strength should be prescribed. Obesity should be avoided or corrected. Hypochromic anemia is common and may respond to sulfate or gluconate or iron, taken orally. However, the mechanism of anemia in this disease is surely more complicated than that of ordinary iron deficiency, so that correction may require transfusions or intravenous injections of iron salts.

The purposes and procedures outlined above center on the provision of optimal hygiene for patients with a generalized inflammatory illness. Such measures are chiefly supportive or defensive, although the effect of salicylates probably transcends into the realm of specific antiphlogistic pharmacology. This quality has also been ascribed to a number of other drugs which are not acceptable to the basic regimen for rheumatoid arthritis. Some of these, like cinchophen compounds, mechlorethamine hydrochloride, or phenylbutazone, require further study of presumably marked toxic potentials and more convincing tests of their practical superiority to salicylates; others, known to be hazardous, nevertheless have a measure of usefulness.

Gold Salts.—Extensive clinical trials indicate that chrysocompounds suppress the activity of rheumatoid disease in some patients (Freyberg). This action probably is not due to a hepatotoxic influence, but to a selective accumulation of gold in, and its direct lethal effect on, inflamed reticuloendothelial cells. The soluble salts, gold sodium thiomalate (Myochrysine), aurothioglucose (Solganal) and gold sodium thiosulfate (Sanochrysin) are widely used for parenteral administration and contain from 37% to 50% of the metal. The material is quickly absorbed but very slowly excreted after intramuscular or intravenous injection, mainly through the kidneys. Colloidal gold is unsuitable.

The prime indication is active peripheral rheumatoid arthritis. Contraindications are severe diabetes mellitus, disseminated lupus erythematosus, nephritis, blood dyscrasias, impaired liver function, hemorrhagic diseases, pregnancy, and history of exfoliative dermatitis. Therapy should begin with two weekly injections of 5 mg., followed by two weekly injections of 10 mg. and of 25 mg., each, until the maximal dose of 50 mg. of the salt per week has been reached in the seventh week. Benefit from chrysotherapy is usually not evident prior to this time, and barring certain complications, treatment should be continued for six months before it may be said to have failed. When there is definite clinical and laboratory evidence of decreasing rheumatoid activity, the injections may be gradually spaced over periods of two weeks and a month. Chrysotherapy may then be discontinued about six months after the disease appears to be inactive.

Untoward reactions occur in 10% to 40% of treated cases. Like other heavy metals, gold is plasmatotoxic, but its preferential absorption by inflammatory tissues probably affords a measure of protection to those parts of the reticuloendothelial system, such as bone marrow, liver, kidneys, and spleen, which would normally be first concerned with the metabolism of gold. Animal experiments suggest that the epithelium of the kidney tubules develops some immunity to gold if treatment is begun with small doses; yet one will frequently encounter evidence of mild renal irritation. Unless albuminuria exceeds 2+ or continues, it is not a contraindication to further treatment, but hematuria and cylindruria call for an intermission. Next most frequent toxic signs pertain to necrobiosis of mucous membranes and skin. They may range from small ulcerations of the oral mucosa to exfoliative dermatitis and can sometimes be anticipated by warning signals, such as canker sores or a sensation of scalding in the mouth or pruritus. Prior to each injection the patient should be questioned and examined for evidence of dermatitis and mucositis. In their presence, treatment should be temporarily withheld and then resumed at half the previous dosage level. There may also be serious damage to the bone marrow; blood cell counts should be performed before and biweekly during chrysotherapy. Treatment should be discontinued permanently when there is evidence of progressive leucopenia, agranulocytosis, or thrombocytopenia. Neuritis due to gold has been reliably reported but is not a common risk. In some cases, chrysotherapy has been followed by hepatitis. Although it is not clear whether this complication results from gold, treatment should be discontinued in the event of liver disease. Gold is accumulated in the body and eliminated for many months or years. Patients on chrysotherapy should be warned against exposure to ultraviolet rays and to sunlight. Toxic reactions can usually be relieved by injection of dimercaprol (BAL), which the physician using chrysotherapy should hold available.

Corticosteroids.—Glucocortical hormones are some of the most effective anti-inflammatory agents known. There is no evidence that inhibition of a rheumatic process by corticosteroids is part of their physiological role. Rather, it appears to be a pharmacologic result which obtains with inflammation due to various stimuli: allergic, thermal, traumatic, infectious, or chemical. The action is known to be topical, and it results also from local application of synthetic steroids which are related to cortisone and hydrocortisone, but do not seem to occur naturally in man.

The endogenous hormones, when given systemically by mouth or injection, are capable of exerting a dephlogistic effect on rheumatic lesions for a variable length of time. Eventually, however, they cause an endocrine imbalance (Fredell and others) which either curtails the specific pharmaceutical benefit or adds risks far greater than those which attend rheumatoid disease not treated by these hormones. Some of the untoward reactions may also be due to pharmacologic mechanisms, and some of the clinical amelioration observed in rheumatoid patients probably stems from endocrine or pharmacodynamic stimuli, both unrelated to the anti-inflammatory action of corticoids. Most of the questions implied here cannot yet be answered; but clinical investigation to date has failed to prove the usefulness of cortisone for the general management of rheumatoid patients in medical practice (Empire Rheumatism Council). One can assume that this would also be true of hydrocortisone and of corticotropin. The synthetic steroids prednisone and prednisolone have anti-inflammatory activity several times that of their natural analogues in equal milligram doses. Their clinical evaluation began less than two years ago (Bunim, Pechet, and Bollet). It appears that they have some of the major hormonal effects of corticoids, for example, depression of adrenocortical function, as well as some of the toxic ones, such as the promotion of gastrointestinal hemorrhages and of emotional instability. Contrariwise, they do not in presumed clinical doses effect sodium retention and potassium depletion to the same degree as do the natural hormones. The discovery of prednisone and prednisolone has demonstrated the possible dissociation between beneficial antirheumatic and undesirable metabolic effects by chemical alteration of corticoids, but their role in the general clinical management of rheumatoid arthritis is as yet uncertain.

Antirheumatic steroids are indicated only under special circumstances. These are instances of fulminating rheumatoid disease characterized by severe constitutional symptoms; also specific complications which carry a significant risk to life or to the function of vital organs, such as iritis and pericarditis; and intercurrent stressful procedures of major surgery or rehabilitation. Under such conditions, corticosteroids may be given for a predetermined period, usually not exceeding six weeks. Of the preparations currently available, prednisone and prednisolone have the highest ratio of anti-inflammatory efficacy to toxic side-effects. In situations postulated here, one should begin treatment with 40 to 60 mg. daily in four to six equal doses. There will be as a rule no need for restricting salt and water intake or for the administration of supplemental potassium. Although all patients on steroid therapy will have close supervision for reasons stated above, they should also have frequent checks on weight and blood pressure and for the detection of glycosuria or of gastric symptoms which may presage the onset of intestinal hemorrhage. It is necessary to discontinue steroid treatment gradually over a period of about three weeks, and while the need for stimulating endogenous production of corticoids under the circumstances envisaged has not been proved, the administration of corticotropin during withdrawal seems entirely rational. Daily administration of 40 units of a long-acting preparation for a period of two weeks may be timed to overlap with the reduction of steroids.

Topical administration of hydrocortisone or prednisolone has attained practical merit as an office procedure (Hollander). These hormones are highly effective in situ and are almost completely and immediately utilized during the suppression of the local inflammatory process. Intra-articular injections are useful where active lesions of rheumatoid disease may be concentrated in but a few joints. Septic arthritis is an important contraindication to this form of therapy. Rheumatoid patients treated by intra-articular corticoids should be cautioned against injudicious exertion of symptomatically improved joints.

Physical Medicine.—For the secondary prevention of crippling deformities, physical therapy is the most essential method, and of various modalities, exercise ranks first in importance (Baker). During severely acute arthritis, it may be confined to muscle setting and assisted active motion. In subacute cases, active exercises are usually beneficial and, depending on the tolerance of individual patients and joints, functional practice may be increased by resistive procedures. Hydrotherapy is extremely helpful in graduation of exercises. Motion alone serves only to stretch muscles and to maintain the range of a joint. More profitably, exercises done by the patient will tend to overcome atrophy both of muscles and articular structures and will aid in the maintenance of muscular tone, which is a prerequisite to the prevention of deformities. In general, muscular exercises should be performed deliberately and to the fullest tolerable range. They should be repeated five to eight times, or less often if undue pain persists for an hour. If a patient can perform this number of

repetitions readily, the load rather than the number of exercises should be increased. This may be accomplished by manual resistance or by the use of weights, pulleys, sandbags, and other mechanical devices.

Most patients will not be able to exercise unless their arthritic pain is adequately controlled. To this purpose salicylates are indicated, but physical measures as well contribute substantially to the relief of spasm. Gentle, stroking massage may be applied to muscles, and heat, particularly, is effective. Used locally over muscles and areas surrounding an inflamed joint for about 30 minutes, it acts as a counterirritant and decreases automatic contractures. Applied systemically to the total body or a large area, it relieves painful congestion. Local heat may be given by simple radiation from a reflector lamp fitted with a 100 watt bulb at a distance of about two ft., or by hot towel packs, hydrocollators, or by immersion in hot water baths or paraffin. If a larger body segment, for instance, an extremity, is to be included, a number of 60 watt bulbs may be installed in a tin reflector which can also be constructed in a size sufficient to cover one aspect of the total body. The temperature of a therapeutic bath should not exceed 95 F (35 C) in the beginning, and may gradually be raised to 102 F (39 C). With general body heating, the patient's pulse should be observed for undue acceleration and irregularities, and he should be protected against accidents resulting from dizziness or loss of consciousness due to sudden vasodilation. There is as a rule no indication for the use of diathermy or ultrasonics in rheumatoid arthritis.

At the outset of any regimen in physical therapy, not only the directions but also the reasons for such measures must be explained to the patient. It will usually be necessary for a technician to instruct the patient until he has obtained adequate understanding and physical awareness of the processes involved in therapeutic exercises. This introduction is more effective than giving a list of exercises. Physical therapists may not be available for continuous treatment, but in most areas their occasional services can be obtained through an agency, such as the Visiting Nurse Association. It may be desirable to have the patient consult a specialist in physical medicine, and he or the attending physician should clearly state the prescription for physical therapy, to include the diagnosis, the parts and body areas to be treated, the modalities, frequency and duration of application, and the intervals at which the patient is to be checked by the physical therapist and by the attending physician.

Orthopedic Measures.—In the presence of active synovitis, ambulatory patients require protection against the functional strains of weight-bearing and motion. This may be afforded by crutches or canes, bandages, or by splinting and bracing. Open casts for support on rest are particularly suitable for knees, wrists, feet, and elbows. Special braces with joints may be provided for hands, knees, and ankles. When the arthritis involves metatarsal-phalangeal joints, arch supports made of metal or rubber may be indicated. Mechanical traction is of considerable value in the management of cases which have come to rehabilitative procedures and as part of their treatment in a hospital. For ambulatory patients and under home conditions, it is apt to be ineffective, and unsupervised traction may cause dislocations and fractures. Orthopedic surgery is one of the neglected aids to the management of chronic rheumatoid arthritis. When the degree of destruction in a peripheral joint has advanced so far that repair or functional recovery cannot be expected, the elimination of motion by arthrodesis may provide the patient with a stable, painless extremity. This indication frequently applies to the ankles or wrists, whose stabilization may indeed prevent spastic deformity of more distal joints. Plastic operations designed to restore motion have been successfully performed on hips, shoulders, elbows, and knees. Excision of deformed and painful metatarsal-phalangeal joints may enable patients to resume walking. In some instances of long-continued synovitis without ankylosis, synovectomy will permit evacuation from the articular space of nonabsorbable debris, and under favorable conditions the synovial membrane will reform in a few months with a better prospect for physiologic function.

Conclusions

Concluding this outline one could rightly observe that the subject matter has not changed much in the last decade or so. Few and minor practicable measures have been added. Less dramatic than experimental drugs, the methodology of managing rheumatoid arthritis has improved, thanks chiefly to more knowledge of its natural behavior. This needs much further study by systematic, long-term research. There is, however, one effort, apart from the exercise of sound clinical judgment, by which physicians may immediately advance the control of rheumatoid arthritis: the development in their communities of technical aids. If the citizen-doctor will insist on ancillary services for rheumatoid patients as he has helped provide them in other types of illness, he will inci-

dentally save his alter ego, the practicing doctor, some time and frustration.

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Case Reports

GUMMA OF LIVER WITH CALCIFICATION

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ACCORDING to Rolleston (1929) the liver is the commonest internal organ to harbour a gumma. The clinical diagnosis of hepatic gumma, however, is rarely made, and subsequent to the report of Tucker and Dexter (1946), who described two cases and were the first to record the effect of penicillin in late hepatic syphilis, we have been able to find reports of only two further cases, Nicol and Terry (1951) and Viranuvatti and Kochaseni (1953), in which the diagnosis was made during life.

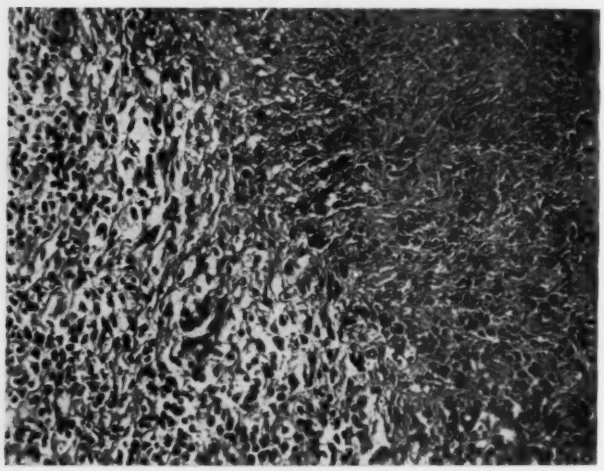

Fig. 1.—Section of liver; × 105.

A third case was reported by Shapiro and Weiner (1951), but the diagnosis was only made after death. The following case presents certain unusual features and was thought to be worthy of description.

A 29-year-old lorry driver attended his own physician in September, 1952, complaining of a painless swelling in his right hypochondrium. He was referred to the surgical outpatient department of a general hospital, where the swelling was thought to be a hematoma lying deep to the sheath of his right rectus adbominis. This confirmed the patient's own view that he had damaged a muscle while indulging in his hobby of weight lifting. The swelling, however, increased in size, and he was admitted to hospital in December, 1952, with a view to surgical exploration. At this time he was recorded as having a "swelling right upper rectus in abdominal wall, not attached to skin. Liver not palpable." At operation two days later the swelling was found to be intraperitoneal and consisted of a hard mass in the liver. The appearance suggested a neoplasm rather than an inflammatory lesion. Several pieces were removed for section. The pathologist reported "a benign necrotic lesion, probably a gumma." At this stage a Wasserman reaction was performed and was found to be strongly positive.

I first saw the patient as an outpatient some three weeks after operation and admitted him to hospital for further investigation and treatment.

Examination revealed a well-nourished man with a recent but soundly healed right subcostal scar. There was noticeable bulging of the right lower ribs. The liver was enlarged to several fingerbreadths below the costal margin and was firm and smooth. There was no collateral evidence of either acquired or congenital syphilis and no history of infection. The blood Wassermann reaction was positive on repetition, but the cerebrospinal fluid was normal in all respects.

It was decided to commence treatment with potassium iodide, 20 grains (1.3 gm.) three times

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a day, and to investigate the patient's liver function prior to instituting more vigorous antisyphilitic therapy. Serum bilirubin, plasma proteins, albumin/globulin ratio, and serum alkaline phosphatase were all within normal limits. On the other hand, the galactose-tolerance and hippuric-acid-excretion tests gave abnormal values, indicating some impairment of liver function. An unexpected finding at this time was the presence of scattered areas of calcification throughout the liver substance as seen on abdominal x-ray.

Treatment was continued first with a suspension

Fig. 2.—Section of liver; ×35

Fig. 3.—X-ray showing intrahepatic calcification prior to treatment.

Fig. 4.—X-ray showing increased calcification nine months later.

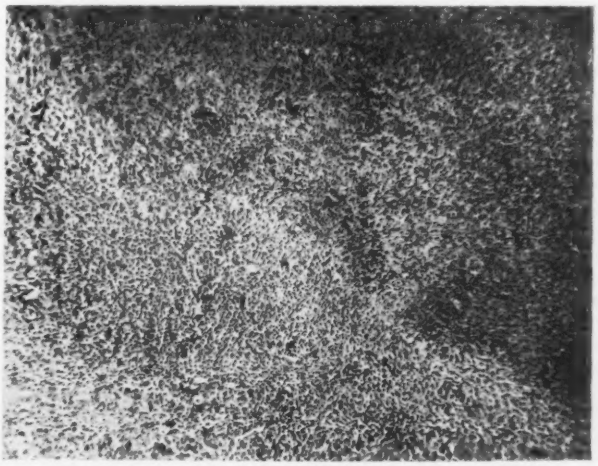

Figure 2

Figure 3

Figure 4

of bismuth oxychloride (Bisoxyl), 0.1 gm. twice weekly, and subsequently with procaine penicillin in oil with aluminum monostearate (PAM), 600,000 units twice weekly to a total of 6 mega units. The total dose of bismuth oxychloride was 1.2 gm.

After treatment the liver became smaller, but two and a half years later the liver edge can be readily felt a couple of fingerbreadths below the costal margin. The surface remains smooth, and its consistence firm. Hippuric acid excretion remained abnormally low for several months and did not reach normal limits until some eight months after treatment was initiated. The patient has remained Wassermann-fast despite several further courses of penicillin. On his discharge from hospital in April, 1953, he resumed his employment as a lorry driver and has subsequently remained free of symptoms of any kind. Repeated abdominal x-rays have demonstrated that the foci of intrahepatic calcification increased in density and became more numerous for some six to nine months. In the succeeding two years they have remained apparently unchanged.

Comment

Nicol and Terry (1951) in presenting a case of late syphilis of the liver comment upon the rarity of gummatous involvement of the liver in late acquired syphilis. Such a view, however, is not borne out by autopsy statistics. Hahn (1943) found 66 examples among 14,561 autopsies carried out at the John Hopkins Hospital between the years 1908 and 1941. Similarly, Symmers and Spain (1946) found 102 examples of hepar lobatum among 23,792 autopsies at Bellevue Hospital. In an earlier investigation Symmers (1916) had encountered hepar lobatum 50 times in 314 cases of late acquired syphilis—an almost unbelievably high proportion. Hahn (1943) in an analysis of 1165 autopsies of adult syphilitics gives an incidence of 4.9% for late syphilis of the liver and comments that in late syphilis involvement of the liver, as determined by autopsy incidence, is second in frequency only to involvement of the aorta and central nervous system.

This is in sharp contrast to the number of cases diagnosed. Bockus (1946), in a decade of study at the Graduate Hospital of the University of Pennsylvania, was unable to establish a diagnosis of tertiary syphilis of the liver in the living patient. In a series of 102 autopsy-proved cases reported by Symmers and Spain (1946), the diagnosis was made during life in 3 cases and was suspected in 1. In another series, of 79 cases (Shapiro and Weiner, 1951), the diagnosis was strongly suspected in 3 cases and discovered in 2 others, once with a peritoneoscope and once during a splenectomy for Banti's syndrome.

The discrepancy between the incidence of gumma of the liver as diagnosed clinically and as discovered at autopsy is only in very small part the fault of the clinician. "Late syphilis of the liver is essentially a focal process, and in an organ with the functional reserve and capacity for regeneration of the liver, a focal process is unlikely to produce symptoms either of hepatic insufficiency or portal failure unless unusually extensive or so located, i. e., at the hilum, as to interfere either with the portal circulation or the excretion of the bile" (Hahn, 1943). Late syphilis of the liver is in fact a frequently benign process which runs its course without giving rise either to symptoms or to clinical signs. Where, however, either because of location or because of the extensive nature of the process, hepatic syphilis does produce symptoms, such symptoms and signs as may occur may be indistinguishable from those produced by other pathological processes affecting the liver, in particular cirrhosis occurring in the syphilitic patient.

Calcification of the liver is uncommon. Konzellman * found only one example of massive calcification in a series of 8000 autopsies. Of cases described in the literature, the majority are due to calcification occurring in the walls of hydatid cysts (Astley and Harrison, 1949; McCullough and Sutherland, 1941). If, however, calcification of the liver is uncommon, calcification occurring in hepatic gummata must be exceedingly rare. It is not mentioned by Shapiro (1951) or Symmers (1946) as occurring in their large autopsy series,

* Konzellman, F. W.: Personal communication to Heibrun and Klein (1946).

while Hahn (1943) states explicitly that he did not encounter it in a single instance. Heilbrun and Klein (1946) state that calcification does not occur in syphilitic cirrhosis, but Gray (1944) cites Henke and Lubarsch (1931) as authority for stating that trabecular calcification and bone formation occur and that calcium may be deposited in gummatous lesions. Smallwood and co-workers (1955) have recently described the occurrence of widespread calcification in the liver of a woman aged 47. There was a history of intravenous injections at the age of 13. Blood Wassermann and Kahn reactions were weakly positive. Casoni's test and complement-fixation test for hydatid disease were negative. They conclude that "whilst favouring the view that the underlying lesion is gummatous this must at present remain speculation." Heilbrun and Klein (1946) have reported a very similar case on the basis of alveolar hydatid disease despite negative Casoni test and repeatedly negative complement-fixation test for Echinococcus and repeatedly strongly positive Wassermann reaction. Their conviction that calcification does not occur in syphilitic cirrhosis, to which we have already referred, led them to exclude syphilis as a possible cause. In our opinion, it would be reasonable to regard both these cases as examples of the same pathological process described here. To what extent treatment in the present case may have influenced the degree of calcification must remain a matter for speculation.

Summary

A case is described of calcification occurring in gumma of the liver.

The pathological anatomy of late hepatic syphilis is discussed in relation to diagnosis.

Intrahepatic calcification with particular reference to syphilis is discussed, and the literature is briefly reviewed.

Mr. W. Lee, of the Department of Photography, Liverpool University, prepared the photomicrographs. Mr. R. J. Ousby cooperated in following up the patient and prepared the Chart.

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EMBOLIC OCCLUSION OF PATENT FORAMEN OVALE

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THROMBOPHLEBITIS followed by pulmonary and later systemic embolism should arouse suspicion of a patent foramen ovale, particularly if the heart itself appears unlikely as an additional source of embolism. Sudden death after such a sequence of events may be precipitated by embolic occlusion of the foramen ovale. This syndrome has recently been emphasized by Elliott and Beamish.[1] These authors stressed the lack of significant electrocardiographic changes in the syndrome. The following case is reported to indicate that such changes may occur and cannot be used to exclude the presence of this syndrome.

Report of Case

A 49-year-old obese woman entered Episcopal Hospital on July 11, 1955, because of shortness of breath. For many years she had not been able to lie flat in bed without dyspnea. One month previously she had begun to experience shortness of breath on effort. She consulted her physician, who found no evidence of disease. A reducing diet was prescribed but not followed. Shortness of breath increased and was accompanied on rare occasions by an oppressive sensation substernally. The entire night before admission to the hospital she had had to sit up because of severe shortness of breath, which finally became so intolerable that hospitalization was advised.

Intermittently, during a period of two years, she had noted slight swelling of her ankles at the end of a day. She gained weight after her marriage, at the age of 16 years, and, in recent years, she maintained a weight of 240 lb. Menarche occurred at the age of 15 years. Menstrual periods were regular in occurrence, every 30 days, and were of 4 days' duration. There were infrequent menstrual clots. She had had four uneventful pregnancies. Systemic review was otherwise negative.

On admission, she was pale, cyanotic, dyspneic, and tachypneic but alert and responsive. The blood pressure was 110/80. Fundoscopy revealed normal findings. The jugular veins were distended on recumbency only. The cardiac impulse was not palpable. The heart sounds were decreased in intensity, but the differential pitch was maintained. P_2 was louder A_2. There was sinus rhythm at a rate of 108 per minute. The lungs were clear. The abdomen was huge but otherwise normal to physical examination. Pelvic examination was negative. There was pitting edema (+1) of the left leg and of both feet. There was slight tenderness of the left calf.

The hemoglobin was 7.6 gm. per 100 ml.; hematocrit, 30 vol. %; erythrocytes, 3,330,000 per cu. ml., and platelets, 89,100 per cu. ml. The total leucocyte count and the differential smear were normal. The concentrations of glucose, urea nitrogen, bilirubin, and cholesterol in the blood were normal. The prothrombin time was also normal. Repeated urinalyses were negative except for an occasional trace of protein. The serological tests for syphilis were negative. Sternal bone marrow examination disclosed normal cellularity, with a slight increase in the erythroid series.

Roentgenographic studies of the chest were made on July 12 and July 19. The cardiovascular silhouette appeared normal. The pulmonary vascular markings were not unusual. The lung fields were clear.

An electrocardiogram on July 12 (Figure) showed sinus rhythm at a rate of 125 per minute. The P-R interval was 0.14 second. The P wave was slightly decreased in amplitude, and the mean P vector was directed 58 degrees anteriorly. The duration of the QRS complex was 0.08 second. The mean QRS vector was directed 30 degrees posteriorly. There was a small S wave in Leads I and aV_L, and there was a small Q wave in Leads III and aV_F. The terminal QRS vector was directed 122 degrees posteriorly. The take-off of the ST segment was slightly depressed in Leads aV_L and I and elevated in Leads aV_F and III. The T wave in the extremity leads was increased in volt-

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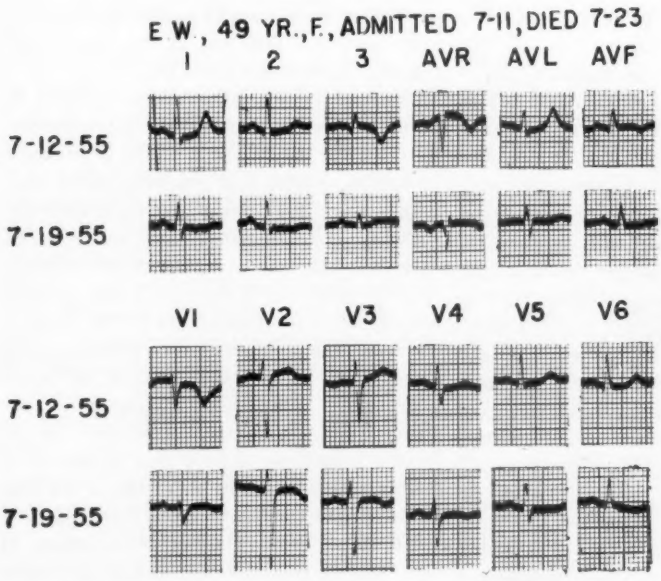

The initial electrocardiogram is considered consistent with acute right ventricular myocardial ischemia due to pulmonary embolism. Note the S wave in Lead I and the Q wave and inverted symmetrical T wave in Lead III. Note also the inverted symmetrical T wave in Lead V_1. The second electrocardiogram shows a slight shift of the mean axis of QRS and a greatly decreased voltage of the T wave.

age and appeared symmetrical. The mean T vector was directed —20 degrees anteriorly. The corrected Q-T interval was 0.52 second. The electrocardiographic findings were considered consistent with acute right ventricular myocardial ischemia.

Anticoagulants were not administered because of the anemia and thrombocytopenia. Elastic stockings were prescribed and worn.

During the patient's hospitalization she had a low-grade fever and occasional tachycardia, with heart rate up to 160 per minute. Oxygen failed to banish her cyanosis. However, dyspnea decreased. Occasionally, she complained of pain in the loins.

An electrocardiogram on July 19 (Figure) showed that the mean QRS vector had shifted slightly to the right and was now directed 60 degrees posteriorly. The T wave was greatly decreased in voltage.

She appeared to be improving, except for persistent cyanosis and slight tachypnea, until July 23, 1955, when, while being moved from the bed to a chair, she suddenly developed intense cyanosis and distention of the jugular veins and died.

Necropsy Findings (Dr. Alan Wallis, pathologist, Episcopal Hospital).—The heart weighed 540 gm. There was a moderate amount of epicardial fat. The myocardium was normal. There was no valvular lesion. The coronary ostia were slightly narrowed by atheromatous plaques. There was minimal arteriosclerosis of the coronary arteries.

Astride of and completely occluding the foramen ovale was a cylindrical thrombus, 5 cm. long and 1 cm. wide. The main pulmonary artery was the seat of a large thrombus, 6 by 2.5 cm. The right pulmonary artery was completely blocked by a large thrombus. Many smaller thrombi were found in the subdivisions of the left pulmonary artery supplying both lobes of the left lung. There was no significant pulmonary congestion. There was no evidence of pulmonary infarction. The cortex of the left kidney had a solitary area of infarction, 2 ml. in diameter. The pelvic organs were normal.

The anatomic diagnosis was (1) peripheral thrombophlebitis, (2) massive and multiple pulmonary embolism, (3) renal infarction and (4) embolic occlusion of a patent foramen ovale. There was no obvious cause for the anemia and thrombocytopenia.

Comment

Our patient had peripheral thrombophlebitis followed by multiple pulmonary emboli. She appeared to be improving, except for persistent cyanosis and for almost constant pain in the loins due to renal embolism. Death occurred abruptly, with intense cyanosis and distention of the jugular veins.

This clinical picture is characteristic of embolic occlusion of a patent foramen ovale. Thirty-four such cases have been reported since 1926.*

The rarity of the diagnosis may be due to the lack of awareness of the syndrome and also because conditions necessary for its development may be uncommon.

* References 1 and 2.

This syndrome can occur only if the following conditions are fulfilled:

First, the opening of the foramen ovale must be sufficiently large to permit lodging of a clot from a peripheral vein and yet not large enough to permit passage of the clot without occlusion. Such a patency (0.7 cm. in diameter) occurred in 6% of the hearts studied by Thompson and Evans.[3]

Secondly, the flow through the foramen ovale must be from right to left. Such a direction of flow may be due to pulmonary hypertension produced by pulmonary embolism. This type of flow permits systemic embolism by clots small enough to pass readily through the foramen ovale. Thompson and Evans [3] estimate, on the basis of their own observations and the work of Haggart and Walker,[4] that over one-third of the pulmonary circuit must be occluded by pulmonary embolism for paradoxical embolism to occur when the foramen ovale is of so-called pencil patency. Obviously, the pulmonary embolus must not be large enough to produce death by itself.

Right-to-left flow through the foramen ovale may also be due to small transient reversals of the pressure gradient [5] or due to jet-like flow directly from the inferior vena cava.[6] Finally, such flow may also be due to any abnormality producing hypertension within the right heart, even when pulmonary embolism is absent. Indeed, about one-half of all cases of paradoxical embolism occur in the absence of pulmonary embolism.[3]

Although the postmortem findings permit ready reconstruction of the sequence of events and the syndrome is characteristic, clinical diagnosis is made with difficulty, if at all, and only after much circumspection. This difficulty is due to the variability of the manifestations and course of pulmonary embolism itself and the difficulty of excluding lesions of the left heart in the presence of pulmonary and systemic emboli. Indeed, Fruhling and Marcoux insist that a diagnosis of paradoxical embolism can be made with finality only by the anatomical demonstration of a clot trapped within the foramen ovale with one free end in the venous and the other in the arterial circuit.[2]

Because the interatrial shunt appears to permit decompression of the hypertension of the right heart produced by pulmonary embolism, Elliott and Beamish stated that an electrocardiographic pattern characteristic of acute cor pulmonale does not appear.[1] Yet their only electrocardiographic illustration discloses an S wave in Lead I and a tiny Q wave with inversion of the T wave in Lead III. There is also depression of the take-off of the ST segment in Leads aV_L and I. This scalar tracing is as consistent with pulmonary embolism as its vector translation, which they so interpret. Other authors cited by them supply no electrocardiographic illustrations but speak of strained patterns. The electrocardiogram of our patient also disclosed similar but more marked alterations in the QRS complex. The take-off of the ST segment is similarly depressed, and the terminal vector of the QRS complexes is directed to the right ventricle. These changes together with changes in the T waves strongly suggested the possibility of acute ischemia of the right ventricular myocardium due to pulmonary embolism. On the other hand, the absence of characteristic electrocardiographic changes does not exclude pulmonary embolism whether an interatrial shunt is present or not, for, as has been emphasized by Currens,[7] no single electrocardiographic abnormality is consistently present in pulmonary embolism.

The electrocardiographic changes seen in pulmonary embolism depend not only upon the degree of mechanical obstruction but also upon the time elapsing from the onset of the attack to the taking of the electrocardiogram.[8] The electrocardiographic changes are also influenced by preexisting heart disease, functional cardiac disorders, metabolic and electrolyte imbalances, and digitalis.[9] Murnaghan, McGinn, and White [9] found that only 33 of 92 cases of pulmonary embolism demonstrated electrocardiographic changes characteristic of pulmonary embo-

lism. The major change observed was the appearance of an S wave in Lead I and a tiny Q wave with inversion of the T wave in Lead III. ST-T alterations of variable degree may also be present. The pattern of intraventricular conduction disturbance of the right bundle branch block type with widening of the S wave in Lead I may occur only in the first hour or two after the onset of a major pulmonary embolism.[8] The predominant cause of these changes appears to be dilatation and strain of the right ventricle. Apparently, the degree of arterial oxygen unsaturation has little effect.†

That the electrocardiogram may show changes suggestive of pulmonary embolism in the presence of a shunt with paradoxical embolism is to be expected, because flow from right to left through the shunt depends upon an elevated pressure within the right atrium. The electrocardiogram reflects the acuteness and the degree of this elevated pressure.

Finally, when sudden closure of the foramen ovale occurs in a person with preexisting pulmonary hypertension a further rise of pressure within the right heart ensues, producing abruptly bulging neck veins and marked cyanosis. Additional pulmonary emboli may further intensify the picture. Within moments, the patient is dead.

Summary and Conclusions

The characteristic picture of embolic occlusion of a patent foramen ovale is illustrated by a case report. This syndrome should be suspected in a person without apparent heart disease who develops peripheral thrombophlebitis followed by pulmonary and later systemic embolism with persistent cyanosis and subsequently dies abruptly with intensification of the cyanosis and bulging neck veins. The electrocardiogram may show signs suggestive of pulmonary embolism.

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CAN AURICULAR FIBRILLATION BE BENEFICIAL IN MITRAL STENOSIS?

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AURICULAR fibrillation is generally considered to be a less efficient cardiac mechanism than sinus rhythm. Support for this concept is offered by reports of improvement in the clinical conditions of patients * on conversion from auricular fibrillation to sinus rhythm. Furthermore, as much as a twofold increase in the cardiac output may occur.† In nearly all reports accounts can be found of patients who did not improve. Occasionally conversion to sinus rhythm heralds the general deterioration of the patient's condition. This event is usually explained as being due to emboli or the toxic effects of quinidine. Sometimes no explanation is attempted. The following case report again calls attention to the problem.

A 49-year-old white man with mitral stenosis was admitted to University Hospitals on Oct. 2, 1953, for evaluation for mitral valvuloplasty. He was known to have had a heart murmur for many years. For one year he had noted dyspnea on effort, and in June, 1953, auricular fibrillation was recognized. He was digitalized and maintained on digitoxin, 0.1 mg. daily. There was nothing in the history otherwise to suggest recent progression of the disease.

Examination disclosed the signs of "pure" mitral stenosis. The heart was not excessively enlarged. Calcification in the area of the mitral valve was seen on fluoroscopy. The electrocardiogram revealed only auricular fibrillation and digitalis effect. He was not particularly ill, and the average ventricular rate was 65 per minute; only once did it accelerate to as much as 90 per minute.

When he was under observation, we were limiting mitral valvuloplasty to more severely ill patients and to those with unequivocal recent progression of symptoms. Therefore, we elected to attempt restoration of sinus rhythm and to follow a conservative regimen.

On Oct. 15, 1953, he received quinidine sulfate, 0.4 gm. each two hours for five doses for a total of 2.0 gm., without effect on the auricular fibrillation. There were no toxic symptoms, and the ventricular rate did not rise above 100 per minute. On the following day the dosage was increased to 0.6 gm. each two hours, and after the third dose (1.8 gm.) sinus rhythm was restored. An electrocardiogram, made shortly thereafter, confirmed the presence of sinus rhythm at a rate of 66 per minute. The only abnormalities were digitalis effect and broad notched P waves. There was no detectable quinidine effect.

He was treated prophylactically with quinidine, receiving 0.2 gm. of the ordinary preparation before each meal and 0.4 gm. of a long-acting (enteric-coated) preparation at bedtime. The same dose of digitoxin was continued. The cardiac rate and rhythm remained normal; he felt well and was discharged, leaving the hospital after lunch on Oct. 18, 1953. He drove about 100 miles to his home.

Later this same day, at about 9 p.m., he called to report that he was extremely short of breath and unable to lie down. In addition, he had headache, nasal stuffiness, and generalized aching. The oral temperature was 100.0 F. His family physician administered a sedative, and digitoxin and quinidine were continued according to the discharge instructions. He did not improve and was returned to the hospital on Oct. 20, 1953. The following were noted: dyspnea, orthopnea, distention of the jugular veins, sinus rhythm at a rate of 100 per minute, diffuse pulmonary rales, a tender and slightly enlarged liver, a positive hepatojugular reflux, and an oral temperature of 100.8 F. The body weight had increased by 3½ lb. There was no evidence of a respiratory infection. The chest x-ray revealed that pulmonary congestion had appeared since the film one week before.

The initial treatment consisted of bed rest, sedation, salt restriction, digitoxin (0.1 mg. daily), withdrawal of quinidine, and one injection of a mercurial diuretic. Slow auricular fibrillation had returned by the following morning. The evidence of congestive heart failure promptly disappeared without further treatment, and the patient left the hospital feeling well on Oct. 25, 1953.

He returned on Jan. 6, 1954, and a very satisfactory mitral valvuloplasty was performed. There were no thrombi in the left auricle. The surgeon

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* References 1-11.

† References 12-17.

estimated that the stenotic mitral orifice measured 4×2 mm. The postoperative course was uneventful. At the end of two months he had resumed full-time office work, without symptoms. Auricular fibrillation continued. We elected to attempt restoration of sinus rhythm again. We admit that this decision was partially motivated by curiosity in view of the preoperative experience.

On March 22, 1954, he received quinidine sulfate, 0.4 gm. each two hours for four doses (1.6 gm.). The ventricular rate rose from 88 to 116 per minute. On the following day, he received 0.6 gm. at each dose for a total of 3.0 gm. The ventricular rate did not rise above 112 per minute. On the third day he received three doses, of 0.8 gm., 0.8 gm., and 0.6 gm. (total, 2.2 gm.). After the third dose he complained of tinnitus and giddiness, and he vomited once. Treatment was discontinued without achieving sinus rhythm. He did not develop signs or symptoms of congestive heart failure while receiving quinidine. He has been seen at six-month intervals since, and he continues to have no significant limitation of activity.

Comment

Several possible mechanisms have been advanced to explain congestive heart failure occurring shortly after the onset of normal sinus rhythm. Many instances have been described in which congestive heart failure occurred from the toxic effects of quinidine.‡ We do not think that this was the explanation in our patient, because after successful mitral valvuloplasty even larger doses of quinidine, associated with a rising ventricular rate and mild symptoms of cinchonism, had no deleterious effect on his heart. Obviously, this is not a controlled observation, because between the two courses of quinidine mitral valvuloplasty was performed and two and one-half months had elapsed.

There was nothing suggestive of thromboembolic phenomena. This possibility is remote, because the surgeon found no thrombi in the left auricle.

Ferrer [20] found suggestive evidence that quinidine may have a direct stimulating action on the myocardium. If this occurs in some patients with mitral stenosis, right ventricular output could rise to the point where the obstruction of a tight mitral valve would increase pulmonary congestion. If this were the correct explanation in our patient, we would have expected congestive heart failure to occur earlier, possibly before the conversion of the cardiac mechanism to normal sinus rhythm.

Rabinowitz and associates [21] point out the possible clinical beneficial effects of auricular fibrillation in mitral stenosis, as follows: a) Digitalis can effectively slow a tachycardia with fibrillation, but is relatively ineffective on sinus rhythm. b) Cardiac output in auricular fibrillation is generally conceded to be lower than in normal sinus rhythm. Since the respiratory symptoms of mitral stenosis stem from elevated pulmonary capillary pressure, and since elevated cardiac outputs necessitate elevated left auricular and pulmonary capillary pressures, reduction of cardiac output likewise lowers pulmonary pressures and therefore reduces pulmonary edema formation. c) At a given pulse rate, systole is shorter and disatole longer in auricular fibrillation than in sinus rhythm. Since blood flows through the mitral valve only during diastole, fibrillation may allow upwards of a liter/minute of blood to pass the mitral valve at a given pressure or a decrease of as much as 20 mm Hg pressure in the pulmonary capillaries for a given blood flow.

The pulse rate in our patient when he returned with congestive heart failure and sinus rhythm was 100 per minute. His ventricular rate was only 66 per minute when sinus rhythm was first restored. It is expected that the heart rate increased even more when he exerted himself upon discharge from the hospital. The shortening of the diastolic interval would tend to cause an increase in the pulmonary capillary pressure.

There are several reports which suggest that some patients have responded to the change from auricular fibrillation to sinus rhythm as our patient did. Maynard [9] mentions two who developed respiratory embarrassment and cyanosis, probably at the moment sinus rhythm was restored. They, however, became well rapidly. Hewlett and Sweeney [22] describe a patient with mitral and aortic disease (their Case 8) who appeared to get worse when sinus rhythm was established. Parkinson and Nicholl [4] describe four cases in which heart failure was induced by quinidine. One of these (their

‡ References 4, 18, and 19.

Case 21) seems to be very similar to our patient, because edema appeared for the first time and heart failure got worse after normal sinus rhythm was established. Quinidine was stopped, auricular fibrillation recurred, and the patient steadily improved with digitalis therapy. During the time quinidine was used, digitalis had been stopped.

Summary and Conclusion

The case history of a patient with mitral stenosis who developed congestive heart failure, apparently as a result of being converted from auricular fibrillation to normal sinus rhythm, is presented. It is impossible to say categorically that this patient's congestive heart failure was caused by restoration of sinus rhythm. The clinical facts do suggest it. Several possible mechanisms are discussed. His experience is admittedly rare. Conceivably it occurs oftener than is suggested by the current literature. It is our hope that similar experiences will be reported. If kept in mind, it might be possible to determine whether restoration of sinus rhythm or quinidine itself is the deleterious factor. We made no such effort. Although auricular fibrillation promptly returned upon the withdrawal of quinidine, standard measures for controlling congestive heart failure also had been simultaneously instituted.

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HUMAN INFECTION CAUSED BY THE MIMEAE ORGANISMS

Report of a Case of a Presumably Healed Bacterial Endocarditis Due to Herellea Vaginicola

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THERE HAS been an increase in recognized human infections caused by the Mimeae group of organisms, which were first named and described by De Bord, in 1939.[1] These organisms have been isolated principally from the urinary tract and also from the blood, spinal fluid, soft tissues, pleural fluid, ascitic fluid, and other body specimens. Their special significance is that they may be morphologically identical to the Neisseria organisms. In contrast to the Neisseria organisms, the Mimeae group are not sensitive to the commonly used antibiotics, and consequently it is extremely important to identify these organisms correctly and use the most effective antibiotic in each particular instance.

A case of an apparently healed bacterial endocarditis due to Herellea vaginicola superimposed upon a rheumatic endocarditis is described.

A 19-year-old Negro private was admitted to a military hospital June 5, 1955, with a four-day history of substernal chest pain which was accentuated by deep breathing, coughing, and lying down and which was improved by sitting up. Three days before entering the hospital he developed persistent pains in both knees, hips, ankles, elbows, and shoulders, with no swelling or redness. The patient had dental work performed one month prior to his admission, and during this time he had no cough, upper respiratory infection, chills, fever, or nightsweats.

His family history was not contributory, and his past history as obtained from the patient's mother revealed that at age 10 he had swollen joints and was in bed for two weeks and that it "affected his heart."

On admission to that hospital, the patient was acutely ill with a temperature of 103, pulse 96 and regular. No foci of infection were apparent, and cardiac auscultation revealed a Grade 1 apical systolic murmur and a loud high-pitched systolic murmur at the base with a snapping P_2. The abdomen was rigid in the right upper quadrant, with local rebound tenderness, and liver dullness extended 2 fingerbredths below the costal margin.

He had a white blood cell count of 9500, with normal differential; hemoglobin of 12 gm. per 100 cc., and a corrected sedimentation rate of 40 mm. the first hour. Blood cultures were negative, with only one drawn prior to starting antibiotics. The C-reative protein was 2+ on admission, with an antistreptolysin O titer of 1:1250 which later fell to 1:500.

On the second hospital day he suddenly went into a shock-like state, developed an enlarged liver, and became jaundiced, and bile was noted in his urine. His hemoglobin dropped from 12 to 9 gm. per 100 cc. and his hematocrit from 42% to 31%. He was digitalized, given oxygen, placed on a low-sodium diet, and given blood transfusions to maintain his hemoglobin at 9 to 10 gm. On this regimen his condition improved and the jaundice subsided. Despite further studies, the nature of the sudden anemia was not apparent. On June 7 he was given 600,000 units of penicillin every six hours and 1 gm. of streptomycin twice daily. Cortisone was started June 9 and in addition 0.5 gm. of probenecid (Benemid) was given four times daily, with the penicillin raised to 1,200,000 units every four hours on July 1. At first his temperature dropped to 99 to 100 degrees, but on the 11th hospital day it again rose to above 102 degrees. The antibiotics and cortisone were discontinued July 8, and only digoxin and acetysalicylic acid were maintained, with the patient's temperature ranging between 98 to 100.4 degrees orally.

While under observation he developed a blowing aortic diastolic murmur and his pulse pressure widened with his blood pressure running 140/40, thought either due to a ruptured aortic cusp or secondary to rheumatic aortitis.

He was transferred to Army Hospital Ft. McClellan, Alabama, in August, 1954, and shortly after admission his condition became critical. He complained of substernal pain, developed orthopnea, and his membranes acquired a dusky hue. He had a regular tachycardia of 120 or more and nightly elevations in temperature to over 102 degrees. His heart sounds varied, with an associated gallop rhythm heard in the aortic area and at times also

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in the mitral region. He had apical and basilar systolic murmurs with a basilar diastolic bruit persistent and blood pressure of 140/40/0. He had no railes, hepatomegaly, or edema.

Shortly after admission to the hospital, a series of 10 blood cultures was drawn, with 5 specimens growing H. vaginicola organisms. A culture of the organism was sent to the Third Army Laboratory, and the identification was confirmed. Serum agglutination studies against the organism with both the patient's serum and a healthy control serum in titers from 1:2 to 1:512 revealed no agglutination. Disc sensitivity tests with this organism as reported from the Third Army Laboratory revealed no striking sensitivity to any of the commonly used antibiotics. It was very sensitive to polymixin B; sensitive to streptomycin, erythromycin, oxytetracycline (Terramycin), bacitracin, and nitrofurantoin (Furadantin), and resistant to penicillin and chloramphenicol (Chloromycetin).

A regimen of 2 gm. of erythromycin and 1 gm. of streptomycin twice daily was started Aug. 31, 1954. Intravenous oxytetracycline, 2 gm. daily, was added Sept. 10 and maintained after Sept. 27 as an oral medication. The patient was also given blood transfusions to maintain his hemoglobin between 11 to 12 gm. Because of his slow improvement, 2 gm. of sulfadiazine every six hours was added Oct. 24. His condition gradually improved from September through December, with his temperature becoming normal for periods as long as a week during the last two months.

On Jan. 3, 1955, streptomycin, oxytetracycline, and sulfadiazine were discontinued, and the only antibiotic maintained was erythromycin, 0.4 gm. every six hours until Feb. 10. On Feb. 21 the patient was given oral penicillin, 250,000 units three times daily, and maintained on this prophylactically. Throughout this entire period of hospitalization multiple blood specimens remained sterile on culture. Early in March his temperature became normal and remained so, except during minor upper respiratory infections, over the next five months.

Prior to his transfer from the latter hospital in July, 1955, his heart was compensated with a pulse which was regular and ranged in the mideighties with the patient at rest. His hemoglobin was 14.5 gm., which the patient produced himself without transfusions, and his sedimentation rate remained in the low thirties. His electrocardiogram showed digitalis effect, with left ventricular hypertrophy and subsidence of first-degree heart block. He has been afebrile since March, with his blood cultures remaining sterile and the antistreptolysin O titer in the nonsignificant range. The patient had no chest pain and was comfortable doing light physical activity.

Studies of this organism done both at this installation and at the Third Army Laboratory yielded a Gram-negative pleomorphic rod which on culture produced acid in galactose, xylose, arabinose, and dextrose media. It did not reduce nitrates and yielded a negative oxidase and catalase test. No agglutination studies were done.

This group of organisms of the tribe Mimeae (to mimic) was proposed by De Bord, in 1939,[1] who noted their morphologic similarity to members of the genus Neisseria. This organism was identified on culture in 30% of 147 cases of normal and pathological conjunctival and vaginal secretions in children.* He described three genera whose common features included (*a*) pleomorphism with the diplococcal form predominating on the solid medium and more even distribution of cocci, rods, and filaments in liquid media; (*b*) a modified bipolar staining; (*c*) Gram-negativity with some return of positivity and also encapsulation. The fermentation reactions varied, however, and on this basis there were designated three genera: Mima polymorpha, which does not ferment carbohydrates, with its varient oxidans; Herellea vaginicola, which produces acid with certain sugars; and Colloides anoxydana, which attacks certain carbohydrates producing acid and gas. Only the last reduces nitrates.

Schaub and Hauber [4] described a group of 15 Gram-negative organisms in 1948, of which 10 were obtained from urine specimens and which they found were related serologically. They called this germ Bacterium anitratum because of its inability to reduce nitrates. These organisms were closely related to a group designated B5W,† which were differentiated into 10 varieties through a study of their capsular antigens.

Ewing, in 1949,[7] related those organisms studied by De Bord, Schaub and Hauber, and Fergusen. He was able to show agglutination of the Herellea micro-organism with the Bacterium anitratum antiserum in addition to their

* References 2 and 3.

† References 5 and 6.

similar morphological and cultural characteristics. In addition, it was felt the Mimeae tribe ought be classified as members of the Parvobacteriaceae.

Ninteen cases of human infection were reported involving the tribe Mimeae [8]: 8 of the Mima genus; 10 of Herellea; and 1 of Colloides. Three of the Mima variety were obtained from therapy-resistant cases of "gonorrhea;" nine of the Herellea were from cultures of cerebrospinal fluid following head injury, and the Colloides from a clinical case of gas gangrene.

In 1948, De Bord [9] described a patient with a M. polymorpha meningitis, the organism recovered from a culture of the spinal fluid, who responded to sulfanilamide and was well when seen one and a half years later. Faust and Hood [10] reported a case of fulminating septicemia caused by M. polymorpha var. oxidans, grown from the blood of a patient presenting with a petechial rash and shock-like state who did not respond to penicillin; the patient died 18 hours after admission. M. polymorpha was isolated from the blood and bone marrow of a patient [11] who two years previously had a surgical correction of a congenital heart anomaly. This patient was treated with oxytetracycline and remained healthy four months later. Schuldberg [12] reported an 18-month-old baby who died of an acute infectious meningitis with M. polymorpha grown from the meninges obtained at postmortem examination and who showed organisms resembling N. meningococcus on a smear taken from a skin lesion antemortem.

Of 24 strains of Mimeae isolated by Scott and Mahoney [13] over a period of a year from various clinical specimens including the urinary and upper respiratory tracts, 23 were classified in the Herellea group on the basis of fermentation and morphlogic considerations. The majority of strains were sensitive to chlortetracycline and oxytetracycline but resistant to chloramphenicol and streptomycin. All strains were resistant to penicillin, and there were insufficient data concerning polymixin and neomycin.

Sorrell and White [14] reported a case of endocarditis with multiple bacterial emboli caused by an organism which, though not typical for a Mimeae strain, agglutinated in serum which also reacted with Herellea organisms; it also resembled them morphologically. This specimen was obtained from the blood of a patient prior to his death, and it was thought that the prostate may have been the source of the infection. Townsend and co-workers [15] reported two cases of M. polymorpha infection; one patient presenting a picture of a Waterhouse-Friderichsen syndrome and a second case having a diffuse septicemia with menigitis. Postmortem cultures in the first case from petechiae of the skin and spinal fluid were positive. The second patient had organisms thought to be Neisseria on the basis of the smear and later identified correctly through culture. The second case was treated with sulfadiazine and penicillin with a successful outcome.

A survey [16] was made of the antibiotic sensitivity of six cultures of Mimeae; two of the Mima and four of the Herellea genera. Using the disc technique and based upon the inhibitory zones, the Mima organisms were sensitive to all antibiotics except chloramphenicol, while the four strains of Herellea were in most instances resistant to all except chlortetracline and neocymin. The sensitivity to these two antibiotics was not striking.

Comment

The significance of the close morphologic resemblance between the Mimeae and Neisseria organisms is not in name alone. It is strongly impressed upon the clinician when confronted by a patient with an infectious meningitis where proper bacterial identification must be made and appropriate therapy instituted.

Also, in the case of a Gram-negative intracellular diplococcal urethritis and cervicitis where the diagnosis is very frequently based upon morphological identification alone, therapy-resistant cases may be due to a poor choice of antibiotics because of an error in diagnosis.

The differential through culture methods is the only means of identification which can conclusively distinguish between these two organisms. Sensitivity studies are most important, particularly in the Herellea group, because of the variability of sensitivity and high degree of resistance shown to the commonly used antibiotics. It is to be expected that as this group of organisms becomes more widely known, more frequent clinical identification of this micro-organism will be made.

Summary

A case of bacterial endocarditis caused by Herellea vaginicola and presumably healed is described.

The close morphologic resemblance to the Neisseria organism is emphasized, and its implications are noted.

The variable sensitivity and frequent resistance to commonly used antibiotics mandates appropriate sensitivity studies to determine the proper choice of antibiotic.

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MEDITERRANEAN ANEMIA IN AN ADULT NEGRO

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SINCE Cooley and Lee's description of Mediterranean anemia, in 1925, a voluminous literature has accumulated on the subject. This disease entity, because of its variable manifestations, has been described and discussed under several names—Cooley's anemia, erythroblastic anemia, thalassemia, Mediterranean hemolytic disease, Mediterranean anemia, and Mediterranean hemopathic syndrome. This constitutional hereditary defect in hemopoiesis is manifest clinically as a disease whose severity may vary from exhibiting only characteristic abnormalities of the erythrocytes to being a severe anemia with hepatosplenomegaly, leg ulcers, and bone changes, with fatal termination in infancy or early childhood. The erythocytes characteristically show anisocytosis, poikilocytosis, leptocytosis, and increased resistance to hypotonic saline, with the presence of many target cells. Although this disease occurs usually in persons of Mediterranean extraction, well-documented examples of its occurrence in persons of Indian, Chinese, African, and pure English stock have been reported. Despite the variable clinical manifestations and varied racial incidence of this disease, certain fundamental elements are common to all cases, indicating that all belong to a single entity (Mediterranean hemopathic syndrome). The common aspects of this disease are the following: 1. Its occurrence is usually limited to persons of Mediterranean extraction. 2. A hereditary element is present. 3. Characteristic changes occur in the erythrocytes.

The following case is presented because (1) this disease is rare in adult Negroes; (2) difficulties are encountered in establishing a correct diagnosis; (3) emphasis should be placed on the concepts that this disorder is not primarily limited to children and is not fundamentally a hemolytic anemia.

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Herrmann Hospital and Baylor University College of Medicine.

Report of Case

A 32-year-old Negro woman was first admitted to Hermann Hospital on March 13, 1953, with the chief complaints of "abdominal pain and yellow eyes." The patient stated that she had been in relatively good health until three or four weeks prior to admission, at which time she developed periodic sharp severe cramping pains in the right upper quadrant of her abdomen, which radiated posteriorly to the infrascapular area. At times, the pain was severe and was associated with nausea and vomiting. Two weeks prior to admission, the patient noted the appearance of icterus in her sclera. Subsequently, she noted that her urine was dark and her stools became lighter. The pain and icterus increased, and for five days prior to admission she had experienced chills and fever. She became so ill that hospitalization was advised. She stated that her menstrual periods were severe and lasted from 7 to 10 days and that she flooded considerably, requiring 8 to 10 pads daily. These periods were associated with periumbilical cramps, which radiated to the low back. Review of systems revealed that the patient had lost no weight during the past year, had not been icteric previously, and had noted no blood loss with the exception of her menorrhagia. She had experienced no angina, edema, or paroxysmal nocturnal dyspnea; no cough, hemoptysis, or wheezing; she had noted some indigestion in the form of gas and belching following the indigestion of fatty foods. She had experienced no urgency, frequency, or nocturia. There were no neurological or muscular complaints. Past history revealed that the patient had had the usual childhood diseases and in 1937 had undergone an uneventful appendectomy. In 1940, at age 19, she was found to have an enlarged spleen and was studied at Shreveport County Hospital, where splenectomy was considered, but decided against. In 1946 a bone marrow biopsy was done, but the patient was unaware of the findings. Family history revealed that she was one of three children, her siblings having died at ages 4 and 5, respectively, of "bad blood." The patient was di-

vorced at the time of admission to the hospital, but she had been married and had two uneventful pregnancies. Both children were living. The patient's father was 56 years of age, living and well, and her mother was 49 years of age, living and well. Questioning about personal habits revealed that the patient did not smoke nor partake of alcoholic beverages. She had been working recently as a cook.

On admission, physical examination revealed the patient to be 5 ft. 2 in. tall and to weigh 123 lb. Her temperature was 102 F; pulse rate, 100 and regular, and blood pressure, 100/60. The patient appeared to be an acutely ill Negro woman with Mongoloid facies, a high forhead, and prominent epicanthal folds. Sclera were moderately icteric. Examination of the head was otherwise negative. No nodes were palpable in the neck. The thyroid was not enlarged. The lungs were clear to percussion and auscultation. The heart was normal in size, and there was a Grade 2 systolic murmur audible over the entire precordium. The liver was palpable 4 cm. below the costal margin at the midclavicular line, and the spleen was palpable 4 cm. below the costal margin at the anterior axillary line. There was moderate tenderness and

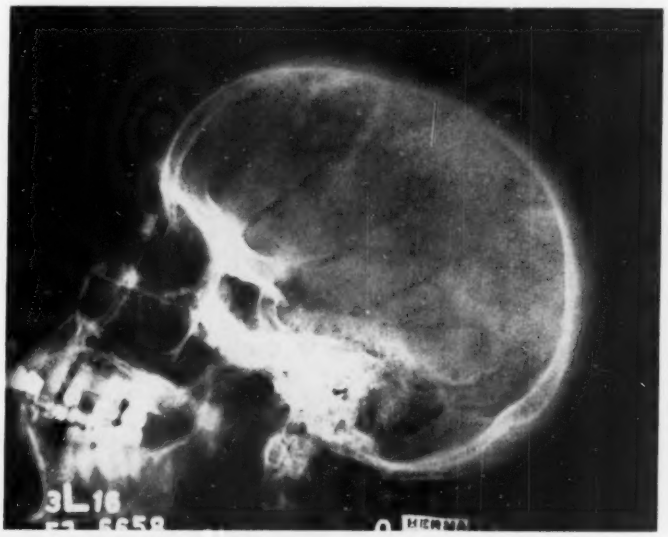

Fig. 1—X-ray showing increased thickness of the diploë associated with increased prominence of the diploic marrow pattern.

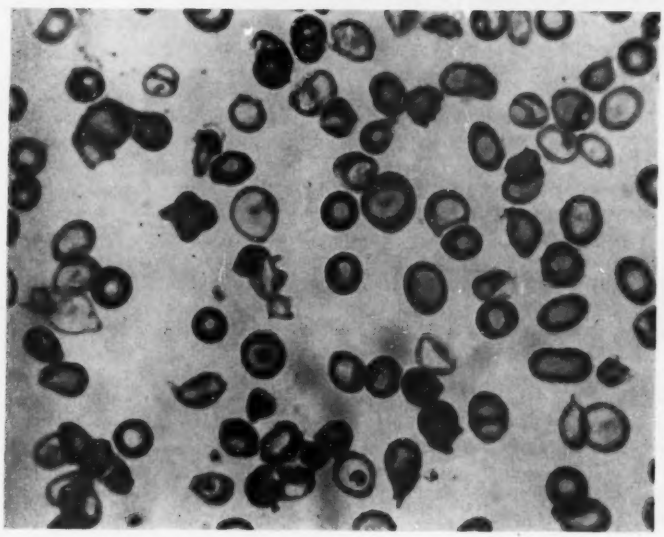

Fig. 2—Stained blood smear showing anisocytosis, poikilocytosis, hypochromasia, and target cells.

muscle spasm in the right upper abdominal quadrant. There was also some midline tenderness in the lower abdomen. Bowel sounds were normal. Pelvic examination revealed a small pedunculated firm mass attached to the region of the right cornu and an 8 to 9 cm. cystic tender mass filling the right adnexal region. Neurological and vascular examinations were negative.

Results of laboratory studies were as follows: Hgb., 8.4 gm/100 cc.; RBC, 3,350,000/cu. mm.; hematocrit value (Wintrobe), 26%; MCV, 78 cu.μ; MCH, 25$\mu\gamma$; MCHC, 32.3%; Reticulocytes, 0.2%; WBC, 6750, with 80% neutrophiles, 2% juveniles, 3% stab cells, and 15% lymphocytes. Stained smear revealed anisocytosis, poikilocytosis, hypochromasia, 8%-10% target cells, and 2-10 normoblasts per 100 leucocytes; sickle-cell preparation, negative; Coombs' test, negative; quantitative (24 hr.) urine urobilinogen, 2.4 mg.; platelet count, 104,000/cu. mm.; bleeding time, 3 minutes 18 seconds; clotting time (Lee-White), 13 minutes 10 seconds; clot retraction time, initial, 40 minutes —complete, 5 hours. Urine analysis: specific gravity 1.018; albumin and sugar negative; 50-60 WBC and 40-50 RBC per h. p. f. Urobilinogen—positive. Bile negative. RBC fragility test: patient, initial hemolysis at 0.40%; patient, incomplete hemolysis at 0.05%; control, initial hemolysis at 0.42%; control, complete hemolysis at 0.34%. Sternal marrow aspiration: hyperplastic marrow with marked erythroid hyperplasia and a reversal of the myeloid ratio of 1:3. Kolmer test, negative prothrombin time, 70% activity. Thymol turbidity, 3.8 units. Alkaline phosphatase, 3.1 Bodansky units. Serum bilirubin, 1.6 mg/100cc.; total proteins 6.2 gm/100 cc. (total albumin 3.3 gm/100 cc. and total globulin 2.9 gm/100 cc.). Fasting blood sugar, 85 mg/100 cc. PA and lateral chest x-ray, Normal Skull x-ray, increased thickness of the diploe associated with increased prominence of the diploic marrow pattern. X-rays of hips and pelvis, normal except for generalized increase in the trabecular pattern of the bones. Electrocardiogram, within normal limits.

Tentative diagnoses were suggested of acute biliary colic, Mediterranean anemia, myomata uteri, and chronic pelvic inflammatory disease. The patient was treated conservatively with penicillin, sulfisoxazole, analgesics, and transfusions. After five days she was free of pain, free of tenderness in the upper right quadrant, afebrile, and only slightly icteric. On May 14, 1953, the patient underwent a total hysterectomy and bilateral salpingo-oophorectomy. Operative findings were uterine fibroids and bilateral salpingitis. On the first postoperative day the patient again became markedly jaundiced, with dark urine; however, the Coombs test was negative at this time and her condition gradually cleared under conservative management. The remainder of her postoperative course was uneventful. The patient was followed in the outpatient department and was readmitted on June 10, 1953, for transfusions. She was admitted to the hospital again on July 29, 1954, because of chills and fever temperature up to 105 F, dark odoriferous urine, dysuria, urgency, frequency, and right costovertebral angle tenderness. Hepatosplenomegaly was present. The laboratory findings remained essentially unchanged, except that urinalysis revealed a specific gravity of 1.005 with 3+ albumin, a few renal cells, and innumerable pus cells. Aerobacter aerogenes was cultured from the urine. The patient was placed on oxytetracycline. Her fever disappeared by lysis, and she was discharged asymptomatic on the sixth day following admission.

Results of subsequent studies were as follows:

1. Gall bladder series. Nonfunctioning gall bladder, without demonstrable gallstones.

2. Oral and intravenous glucose-tolerance tests. Within normal limits.

3. Radioiron turnover studies. On the day of the test, hematological data were as follows: Hgb., 5.8 gm/100 cc.; RBC, 2,200,000/cu. mm.; hematocrit value (Wintrobe), 22%; reticulocytes, 0.6%; WBC, 7250, with 57% neutrophiles, 42% lymphocytes, 1% basophiles; many normoblasts were noted on stained smear.

A dose of 5μ of Fe^{59} as citrate with 6γ of iron was administered intravenously, and the disappearance rate was determined;[10] the results were as follows: Disappearance half-time from plasma, ½ hour; plasma volume, 2950 ml.; radiological hematocrit value, 17%; Plasma iron concentration (average), 125γ/100 cc.

Subsequent radioisotopic analysis of the red cells demonstrated 9% ulilization of the radioiron in three days and 16% in nine days.

4. Radiochromium red cell life span studies. Thirty milliliters of whole blood was withdrawn into a citrated syringe and added to sodium chromate containing 100μ of Cr^{51} with 78γ of chromium. After one-half hour incubation at room temperature, tagging was stopped by the addition of 50 mg. of ascorbic acid,[12] an aliquot removed for analysis, and the remainder of the blood was returned to the patient. Simultaneously, plasma volume was determined with Evans' blue dye. The dilution factors gave these results: Plasma volume, 3200 cc.; red cell mass, 900 cc.; calculated whole body hematocrit value 22%. The survival of the tagged RBC was followed for 45 days. The shape of the survival curve was within normal limits for this technique in our laboratory, 50% of the radiochromium (correcting for radioactive decay) being present in the red cell fraction at 32 days.

5. Electrophorectic analysis of the hemoglobin. No abnormal pigments were present.

Family Studies

The parents, although living and well, were unavailable for study. Examination of blood from the two children revealed the following data:

Daughter, age 16 years: hemoglobin, 13.5 gm/100 cc.; RBC, 34,600,000/cu. mm.; stained smear, 24% leptocytes, 2% target cells, and 76% normal cells; RBC fragility: patient, initial hemolysis at 0.42%; patient, complete hemolysis at 0.28%; control, initial hemolysis at 0.44%; control, complete hemolysis at 0.34%.

Son, age 15 years: hemoglobin, 13 gm/100 cc.; RBC, 35,000,000/cu. mm. Stained smear: 20% leptocytes, 1% target cells, and 79% normal cells; RBC fragility: patient, initial hemolysis at 0.42%; patient, complete hemolysis at less than 0.28%; control, initial hemolysis at 0.44%; control, complete hemolysis at 0.34%.

Further Course

The course of the disease was otherwise not remarkable. Our patient failed to return after her visit of Nov. 5, 1954. At the time of this visit, she was feeling well, her hepatosplenomegaly was unchanged, and her hemogram was as follows: hemoglobin, 9.9 gm/100 cc.; RBC, 34,070,000/cu. mm.; hematocrit value, 32%; WBC, 8600/3 cu. mm. Stained smear: 3 normoblasts per 100 white cells; erythrocytes showed anisocytosis, poikilocytosis, polychromasia, and stippling; there were numerous target cells.

A review of this patient's record from the outpatient department revealed frequent visits, and she usually felt exceptionally well. Upon these various visits, her laboratory data were within the following ranges: Hemoglobin, 7.3 to 10.2 gm/100 cc.; RBC, 33,240,000 to 4,280,000/cu mm.; WBC, 5000 to 14,000. Stained smear: normoblasts and nucleated red cells were usually present, from 4 to 30 per 100 white cells counted 4 to 15% target cells. Anisocytosis, poikilocytosis, polychromatophilia, and stippling always present. Serum bilirubin, 0.5 to 2.5 mg/100 cc.; reticulocytes, 0.5% to 0.4%.

Summary of Case

A Negro woman with rather severe Mediterranean anemia lived a completely asymptomatic life until the age of 19, when splenomegaly was accidentally detected. Subsequently, she was gainfully employed, experienced no incapacitation due to her disease, and was first seen at Hermann Hospital at age 32, because of acute biliary colic and menorrhagia. The menorrhagia certainly contributed to her anemia and was relieved by total hysterectomy. The jaundice caused much confusion at first as to whether it was due to the Mediterranean anemia or to a common duct stone. The subsequent course has proved that a stone with acute biliary colic was the cause. Mediterranean anemia is not punctuated by hemolytic crises of this degree. After that admission, she was seen in the hospital for acute pyelonephritis. Other than at the time of these incidental complicating illneses, the patient was unaffected by her Mediterranean anemia. The diagnosis was established by physical examination, erythrocyte hemoglobin analysis, and family studies. She is in fairly good health at the present time, gainfully employed, and asymptomatic. Splenectomy was decided against, as the red cell survival was normal.

Comment

Mediterranean anemia is frequently characterized by Mongoloid facies; pallor; hepatosplenomegaly; characteristic changes in the skull, pelvic, and long bones; microcytosis; poikilocytosis; polychromatophilia; target cells; normoblasts, and basophilic stippling in the peripheral blood. The erythrocytes show increased resistance to hyptonic saline. The bone marrow is hyperplastic and normoblastic. There is usually mild reticulocytosis, leucocytosis, and icterus. In addition, there are always some manifestations of the disease in other members of the family. Pathological hemoglobins are not present in the pure syndrome. In the severe form of the disease the person usually dies during childhood; however, affected persons may manifest anemia, icterus, and mild hepatosplenomegaly but live a productive, relatively asymptomatic normal life span; or, if only the trait is present, the manifestations may be limited to characteristic changes in the erythrocytes. The fact that many persons with Mediterranean anemia lead a relatively asymptomatic normal existence is not well known; nor is it always realized that this disease may occur in peoples of all racial extrac-

tion. However, it is rare in Negroes.[13] The general consensus regarding the mode of inheritance of Mediterranean anemia is that the severe, fully developed syndrome is inherited as a single dominant gene variably expressed; thus, the homozygous form of the disease manifests itself in the severe classical anemia terminating fatally early in life, and the heterozygous form, only in the characteristic changes in the erythrocytes causing no symptoms.* Although the severe form of the disease is usually manifest early in the life, the milder forms may be seen in patients with all the well-known stigmata of the disease who survive through the fourth and fifth decades. The latter are relatively asymptomatic, manage to be gainfully employed, and may be subject to the numerous diseases of other persons, such as renal lithiasis, leg ulcers, gouty arthritis, peptic ulcer, cholelithiasis, cardiac disease; pernicious anemia, and pernicious anemia of pregnancy.[7] The variability in the severity of this disease has been well discussed by Dameshek.[4]

Severe cases of Mediterranean anemia are so characteristic that they can hardly be missed. The milder forms which survive into adult life and which are relatively asymptomatic may reveal only characteristic red cell changes. The intermediate cases will have splenomegaly in addition to the characteristic blood picture. The symptoms, physical examination, and routine blood studies are usually sufficient to make a clinical diagnosis of Mediterranean anemia. However, to establish the diagnosis conclusively, evidence of the disease in other members of the family must be found, and hemoglobin analysis, using quantitative electrophoretic and alkali denaturation techniques, must be negative for abnormal pigments, except for hemoglobin F, which is frequently found in increased amounts.

The differential diagnosis of Mediterranean anemia resolves itself along the following lines:

(1) Idiopathic hypochromic anemia. This disease is characterized by glossitis, nail changes, achlorhydria, and a characteristic response to iron therapy, which are not present in thalassemia.

(2) Congenital hemolytic icterus. Although very similar to Mediterranean anemia, this condition is rare in Negroes and is always associated with spherocytosis and a decreased resistance of the erythrocytes to hypotonic saline.

(3) Idiopathic, symptomatic, chemical, and immunologic acquired hemolytic anemia. These can be readily excluded by the history, physical findings, and appropriate laboratory studies.

(4) Gaucher's disease, Hand-Schüller-Christian syndrome, lymphomas, malaria, and other conditions producing splenomegaly. These are rather easily excluded by their associated symptoms and laboratory findings.

(5) Lead poisoning. This condition may cause anemia, stippling, target cells, and a course slightly similar to that of Mediterranean anemia; however, urinary and serum lead determinations easily differentiate this condition.

(6) Sickle-cell anemia. This disease is similar to Mediterranean anemia in many respects; however, it is always accompanied by a positive sickling preparation.

(7) Hemoglobin C disease. Clinically, this is a compensated hemolytic process manifest by reticulocytosis and the presence of normal hemoglobin and red cell values. There may be a mild normochromic macrocytic anemia. The marrow is normoblastic. Splenomegaly is present, and numerous target cells are seen in the stained smear. This condition has been found only in Negroes, and hemoglobin analysis reveals large amounts of hemoglobin C.[14]

(8) Sickle-cell-hemoglobin-C disease. Persons with this genetic combination have hepatomegaly and a mild anemia with many leptocytes and target cells. Target cells may comprise 70% of erythrocytes. There is decreased osmotic fragility of the erythrocytes and occasional sickle cells are seen in the smear. Sickle-cell preparations

* References 11 and 18.

are positive. Hemoglobin analysis reveals abnormal pigments S and C.

(9) Certain unusual simultaneous heterozygous combinations of thalassemia and sickle-cell or hemoglobin C pigments. To distinguish these conditions, family studies and hemoglobin analysis are essential. When a person is simultaneously heterozygous for thalassemia and an abnormal pigment (hemoglobin S or C), an unusually large percentage of the pathological pigment may be present in the hemolysate. The hypothesis has been advocated that the thalassemia gene modifies or enhances the expressivity of the gene for the pathological pigment, causing it to be found in large amounts.[15]

(*a*) Sickle-cell-thalassemia disease. Persons with this disease are double heterozygotes, harboring one gene for sickle-cell hemoglobin and one for thalassemia. This combination manifests itself in some persons as a severe hemolytic process, with hepatosplenomegaly, abdominal crises, leg ulcers, and characteristic red cell findings. Occasionally, it may result in a mild, asymptomatic condition. The sickling test is always positive in these persons, as well as decreased osmotic fragility of the erythrocytes. The stained smear reveals microcytosis, hypochromasia, target cells, and a microcytic hypochromic anemia. Hemoglobin analysis reveals sickle-cell hemoglobin to comprise 60% to 88% of the total pigment. A study of the family members reveals sickle-cell disease or of sickle-cell trait in some and manifestations of thalassemia in others.†

(*b*) Hemoglobin-C-thalassemia disease. These persons may manifest a slight anemia with microcytic erythrocytosis and a slight reduction in hemoglobin. Large numbers of target cells are present. Erythrocytes show increased osmotic resistance to hypotonic saline solution, and hemoglobin analysis reveals an unusually high percentage of hemoglobin C (up to 70%). Also, up to 45% of the erythrocytes may be target cells.[15]

† References 16 and 17.

(*c*) Hemoglobin-E-thalassemia disease. This condition is a severe hemolytic syndrome that closely mimics Cooley's anemia in its manifestations.[2] The onset is usually in infancy. These persons may show a microcytic hypochromic anemia of a severe degree. Nucleated red blood cells are prominent, and spherocytes may make up to 8% to 10% of the erythrocytes. The red cell life span is shortened, and hemoglobin analysis reveals hemoglobin E and hemoglobin F.[2]

(10) There are other rare syndromes due to the presence of abnormal pigments, hemoglobins D, E, and H, either as a pure disease, a trait, or combinations of the trait with sickle-cell anemia or thalassemia.[1]

It is obvious that establishing the exact diagnosis of thalassemia in an adult Negro presents a major cooperative task. A study of the family and hemoglobin analysis are essential.

The defect in thalassemia is apparently an inherited inability to synthesize an adequate amount of hemoglobin, probably concerned with the utilization of iron. This is suggested by the morphological blood picture (hypochromia) and by the iron-containing pigment concentrated in the various tissues of afflicted persons. Although persons with Mediterranean anemia are icteric and maintain an icreased reticulocytosis, the evidence of blood destruction in the plasma and urine is never as striking as in the exaggerated erythropoiesis. The manifestations indicating increased blood destruction may be due instead to the breakdown of unused hemoglobin precursors.[5]

The results of the isotope studies using iron and chromium help to confirm this concept of the disease, although in turn presenting other problems as to the basic etiology. The red cell life span obtained by chromium-tagging technique is apparently within normal limits. It is our opinion that the extraneous addition of a foreign ion which tends to have a consistent rate of elution is at best a semiquantitative indicator of life span. Before strict reliance

can be placed on the red cell life spans obtained, confirmation by independent techniques is required in a variety of disease conditions. Pending such data, the results in this patient indicate no gross reduction of life span or evidence for a population of highly abnormal short-lived cells.

The iron turnover studies tend to confirm the reduced rate of hemoglobin production. Normal ranges in this laboratory for iron turnover data are disappearance half-time of one to one and three-quarters hours, plasma iron concentration of 70γ to 120γ/100 cc., and red cell utilization of the tracer iron of 25% to 40% in three days and 80% to 95% in seven days. Alterations of these values in disease are generally predictable in terms of the mechanisms upset. Hypoplastic marrow has lessened need for iron, consequently clearing plasma more slowly and permitting an increased iron concentration and utilizing a decreased percentage of the available plasma iron. Typical values for classical hypoplastic anemia are half-time of three to five hours, iron concentration of 175γ to 200γ/100 cc., and 10% utilization in seven days.

Anemias characterized by increased avidity of the marrow for iron, as iron deficiency, bleeding, or hemolytic anemia, result in rapid plasma clearance, with consequent decreased iron concentration, and rapid complete utilization. Values associated with these conditions are half-time of 15-40 minutes, iron concentration of 0γ to 50γ/100 cc. (30γ to 150γ in hemolytic disease, rapidly variable in a single person), and utilization rates of 95% to 100% in three to five days.

The triad observed in this patient—increased clearance rate, relatively high plasma iron concentration, and poor incorporation in circulating red cells— has been observed by this group in only two conditions, untreated pernicious anemia and thalassemia. The five cases of thalassemia major (in preparation by Daeschner and Loeffler) and the four of pernicious anemia which have been studied in this laboratory have all shown this pattern.

Explanations which have been offered are the following:

1. Iron is cleared rapidly from the plasma by the marrow, but because of the maturation arrest is not released into circulation. This does not account for the continued high iron concentration in the plasma despite the rapid clearance. It also requires that the iron either appear eventually in the circulating blood (which we have not found up to seven weeks in several cases) or that iron continue to accumulate in the marrow and so reach tremendous proportions.

2. Cells with a spectrum of life span, or several discrete populations with differing life spans, are released. Many or most cells break down rapidly, the iron returning to the plasma for return to the marrow. At any time of analysis, most of the iron would be in process of reutilization and only a small percentage in cells of good quality. This explanation also accounts for the high iron concentration. However, if such were the case, greater evidence of and excretion of the products of hemolysis should be typical of these diseases. Further, since the blood should contain an admixture of all cell types at any given time, a sample taken and tagged with chromium should contain a fair proportion of short-lived cells which have just been released. This would result in a very rapid initial drop in the circulating chromium level, followed by a more normal curve. This was not obtained in the present case.

3. The plasma iron is in rapid exchange with a large labile iron store. The rapid disappearance from the plasma represents primarily a transfer to these storage areas rather than to the marrow. These labile stores in turn maintain a high plasma concentration. This, removed by the marrow, would then be incorporated into cells of reasonable life span, but total hemoglobin production would be decreased. The wide

dissemination of iron throughout the body is consistent with this explanation.

Even in the normal person, a portion of the iron leaving the plasma must be transferred to the storage depots. This is inferred from the failure of all of the tracer iron to reappear in red cells except in severe iron deficiency. Additional proof is offered by the torso-scanning studies of Elmlinger.[6] If the last explanation for the triad noted in this disease is correct, the reversible transfer to the storage depots must be abnormal, at least quantitatively and perhaps qualitatively. The disappearance rate from the plasma is much more rapid than normal. That this is not due to the high iron concentration alone is shown by the slow disappearance rate noted in typical hypoplastic anemias, which also show high iron concentration. It is likely that basically different mchanisms are involved, probably owing to a difference in one of the enzymes concerned in the storage of iron or in the control of this storage.

That the last explantion does not account for all the observed abnormalities is evident, since a disorder of the storage mechanism alone would not account for the altred red cell morphology. Nevertheless, it is felt that the evidence is sufficient to offer this theory to explain many of the abnormalities observed.

Other mechanisms are probably involved, and there may be congenital hepatic dysfunction present, since jaundice is present in the absence of increased hemolysis.[3] It is noteworthy that subjects with thalassemia minor have normal red cell survivals[9] and that there is decreased red cell survival in persons with thalassemia major, indicating some degree of increased blood destruction.[8] Mediterranean anemia, although manifesting icterus, is not fundamentally due to a hemolytic process, and the minor degree of hemolysis which occurs, if any, is slow and progressive in nature and is not interrupted by crises. This fact should help one in separating it from the other congenital hemolytic syndromes which manifest hemolytic crises—congenital hemolytic icterus and sickle-cell anemia. Another relevant factor in Mediterranean anemia is the fact that splenectomy results in a spectacular increase in the number of nucleated red cells in the peripheral smear and in no amelioration in the anemia itself.

Summary

The case of an adult Negro with proved Mediterranean anemia is presented. The fact that no race or age is exempted from this malady is been reemphasized. The variability of the disease is commented on.

That a family study and hemoglobin analysis are essential in establishing the diagnosis is stressed. The fact that Mediterranean anemia is primarily a defect in hemoglobin synthesis and red cell production and not a hemolytic process interrupted by crises is emphasized.

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A FAMILY EPIDEMIC OF PSITTACOSIS WITH OCCURRENCE OF A FATAL CASE

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THERE has been a significant increase in the importation and sale of psittacine birds during the past five years following the relaxation, in late 1951, of federal regulations governing quarantine and shipment of these birds.[1] Several recent articles * have emphasized the coincident sharp increase in human psittacosis. The number of cases reported annually to the United States Public Health Service from 1945 to 1951 varied between 25 and 35. This number rose to 135 cases in 1952, 169 cases in 1953, 495 cases in 1954, and 278 cases in 1955.[8]

Parakeets and parrots are considered to be the principle source of human infection [9] although the disease can result from contact with other types of birds.† For example, the 1954 total is high because over 200 cases were attributed to contact with infected turkeys. Considering that many human infections are not recognized or reported, it is significant that over 250 cases in each of the last two years resulted from contact with psittacine birds. An important fact, often unknown to the layman and forgotten by the physician, is that the virus may be disseminated by an apparently healthy bird.‡ Transmission from man to man can occur, but such spread is rare in comparison with spread from bird to man.[16]

This report describes a family epidemic of psittacosis—initiated by parakeet contact—which resulted in the death of the father and infection of three other members of the family. In the latter, manifestations ranged from severe illness to inapparent infection, illustrating the complete spectrum of psittacosis. Psittacosis viruses were recovered from the lung of the fatal case and from a parakeet obtained from the store that sold the infected birds to this family. Data relative to the events in this family and to the handling of love birds by the store are presented to emphasize the hazard of parakeets as pets.

Materials and Methods

Serological studies.—Serum speciments were collected in the hospital and in the home on the date's indicated in the table. Sera were stored at —20 C and transferred to the laboratory in the frozen state. Complement fixation tests with chick embryo (Lygranum) antigen were performed by the Division of Laboratories, Ohio Department of Health. Titer is expressed as reciprocal of the highest initial dilution of serum producing complete fixation.

Virus studies—Lung tissue from the fatal case was stored at —70 C for two days; then an approximate 20% suspension in Hank's balanced salt solution was made with 100 units of penicillin and 0.1 mg. of streptomycin per milliliter. Six mice were given 0.5 ml. of the suspension intraperitoneally; 6 mice were given 0.03 ml. intracerebrally. Mice inoculated intracerebrally started dying within 7 days; those

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† References 10-13.

‡ References 5, 14, and 15.

Summary of Clinical and Serological Data on All Members of the Family

Case No.	Age	Sex	Clinical Illness	Date of Onset of Symptoms	Date of Serum	Antibody Titer*
1	40	M	Fatal pneumonia and encephalitis	6/12/55	6/23/55	160
2	37	F	6-day illness with malaise, fever, weakness, headache, anorexia, myalgia, and nonproductive cough	6/12/55	6/24/55 7/ 5/55 7/28/55	320 160 160
3	16	F	Severe bilateral bronchopneumonia; pregnant during illness	6/13/55	6/24/55 7/ 5/55 7/28/55	640 640 640
4	18	F	3 days of headache, malaise, sore throat, nausea, vomiting, and anorexia	6/13/55	7/28/55	Neg.
5	10	M	None		7/28/55	80
6	14	M	None		7/28/55	Neg.
7	13	M	None		7/28/55	Neg.
8	9	M	None		7/28/55	Neg.
9	8	F	None		7/28/55	Neg.
10	7	F	None		7/28/55	Neg.
11	4	F	None		7/28/55	Neg.
12	2	F	None			

* Reciprocal of initial dilution of serum fixing complement with chick embryo (Lygranum) antigen.

inoculated intraperitoneally, within 10 days. A 20% suspension of brains harvested from mice dying after intracerebral inoculation was introduced into the yolk sacs of 7-day-old chick embryos. All of six embryos given undiluted material died within four days; six given a 1:100 dilution of suspension died within six days. Yolk-sac impression smears stained with Machiavelli stain exhibited inclusion bodies. The Division of Laboratories, Ohio Department of Health, also isolated psittacosis virus from these same lung and mouse-brain suspensions and examined the parakeets for the presence of psittacosis virus.

The Family Epidemic

The Table summarizes the clinical and laboratory data pertaining to the 12 members of the household. The family consisted of a Negro minister, his wife, and their 10 children, 4 boys and 6 girls. The children ranged in age from 2 to 18 years. The family lived in a single, large, clean, well-maintained, seven-room house in a neat residential section. Parakeets were kept in many nearby homes, the enthusiasm for these birds apparently representing a neighborhood fad. On about May 15, 1955, the oldest daughter and a friend purchased two parakeets at a "dime store" in central Cleveland. They did not recall seeing sick birds in the cage from which they made their selection. In the home, the bird cage was kept in the dining room. The job of cleaning the cage was delegated to the oldest girl (age 18, Case 4) and the oldest boy (age 14, Case 6), although the 10-year-old boy (Case 5) cleaned the cage on one occasion. The parakeets stayed in the home for only two weeks, and during this time both birds appeared to be in good health. They ate and drank well, sang normally, had smooth feathers, and did not sneeze. At the end of this period, the birds were put on the back porch in their cage while the family went away for a weekend trip. Upon their return, the cage was found overturned on the ground and the birds gone. The neighbor's opinion was

that the birds had fallen prey to a local dog.

The parents were the first to become ill, both developing symptoms approximately 11 days after their last contact with the parakeets. Symptoms began in the two oldest daughters on the next day. Three of the four persons with symptoms had serologic evidence of psittacosis, and a diagnostic antibody titer was demonstrated in the serum of the 10-year-old boy (Case 5), the child who had cleaned the bird cage only once. The cage was usually cleaned by an older brother (Case 6) who, in spite of his more intimate contact with the birds, developed neither symptoms nor antibodies.

From an epidemiological point of view, the outbreak of psittacosis in this family can most reasonably be interpreted as arising from a common source, namely, the two parakeets. The dates of onset of illness in those persons having symptoms indicate that person-to-person spread did not occur, since the incubation period of psittacosis is 7 to 14 days.

Report of Cases

CASE 1—A 40-year-old Negro man was admitted to University Hospitals on June 23, 1955, with a 12-day history of increasing malaise, weakness, chills, fever, headache, and occasional nausea and vomiting. During the first days of illness he became progressively weak. Tachypnea and delirium appeared on the sixth day of illness. Slight nonproductive cough began two days before admission. On that day he was first seen by his private physician, having refused medical attention until this time. A diagnosis of bilateral pneumonia was made. Hospitalization was recommended but was refused by the patient. He received intramuscular penicillin on that day and the next and reportedly had transient improvement of all symptoms following the first injection. Neck stiffness began on the day before admission. On the next day, rapid deterioration in his condition led the family to seek hospital care in spite of the patient's protest.

Physical examination showed the patient to be acutely ill, with a dry cough and shallow respirations at a rate of 60 per minute. Rectal temperature was 37.8 C (100.04 F), pulse 108, and blood pressure 130/60. He was delirious and moderately dehydrated. A few small vesicles with surrounding erythema were seen on the upper chest. The chest was symmetrical, and expansion was equal bilaterally, although very shallow. There was dullness to percussion over the posterior right chest and over the entire left lung. In these areas the breath sounds were bronchial, and many coarse inspiratory and expiratory rales were heard. The remainder of the physical examination was normal.

The leucocyte count was 64,000, with a differential of 76% neutrophiles, 19% band forms, 2% lymphocytes, and 3% monocytes. The hematocrit was 46%. Urinalysis revealed the following: specific gravity, 1.020; pH, 4.5; albumin, 2+; acetone, 1+; sugar, absent; 5 white cells and many granular casts per high-powered field. The Kline test was negative. Cold hemagglutinins were not detected at a serum dilution of 1:4. Typhoid, paratyphoid, and Brucella agglutinins were absent. There was no growth in cultures of blood and spinal fluid. The cerebrospinal fluid contained a few fresh red blood cells. The protein was 36 mg. per 100 ml., and the sugar was 148 mg. per 100 ml. A chest film (Fig. 1) showed extensive confluent bronchopneumonia involving all lobes, most marked on the left. A small pleural effusion was present in the left costophrenic sinus.

The brief hospital course was characterized

Fig. 1.—Roentgenogram of fatal case of psittacosis, showing confluent bronchopneumonia involving all lobes.

by continued coma, extreme respiratory distress, and death six hours after admission.

Postmortem examination § was done two and one-half hours after death. When the chest was opened, 100 ml. of slightly turbid, yellow fluid was found in the left thoracic cavity, and 50 ml. of similar fluid was found in right thoracic cavity. The pleural surfaces were smooth. The lungs were more than twice normal weight, the right weighing 1040 gm. and the left, 930 gm. Both lungs were firm and noncrepitant throughout, except for minimal aeration of both upper lobes. The cut surface was dark grayish-red, moist, firm, and noncrepitant, with involvement in a lobar distribution. Microscopic examination (Fig. 2) showed practically all alveoli to be filled with cellular exudate, edema fluid, red blood cells, and fibrin. Mononuclear cells predominated, although some polymorphonuclear leucocytes were seen. Many of the mononuclear cells within the alveoli resembled swollen alveolar lining cells. A number of the mononuclear cells contained round or oval cytoplasmic inclusions ranging from less than 1μ to 3μ in diameter. These inclusions were basophilic, were demonstrated by the periodic acid-Schiff stain, and were shown to be DNA-positive by the Feulgen stain. It cannot be stated with certainty whether these cytoplasmic masses represent virus bodies or phagocytized nuclear debris. The alveolar lining cells were swollen and had hyperchromatic nuclei. The alveolar septa were edematous and contained exudative cells. Many capillaries contained fibrin and platelet thrombi. There was some necrosis of bronchiolar epithelium; no inclusions were demonstrated in epithelial cells identified as being bronchiolar in origin.

The cerebrum, mesencephalon, medulla, and spinal cord showed numerous small infarcts, chiefly involving the white matter in relation to thrombotic occlusion of capillaries or arterioles (Fig. 3). There was little glial reaction. Variable cellular

§ Performed by Dr. Hugh F. McCorkle, Institute of Pathology, Western Reserve University.

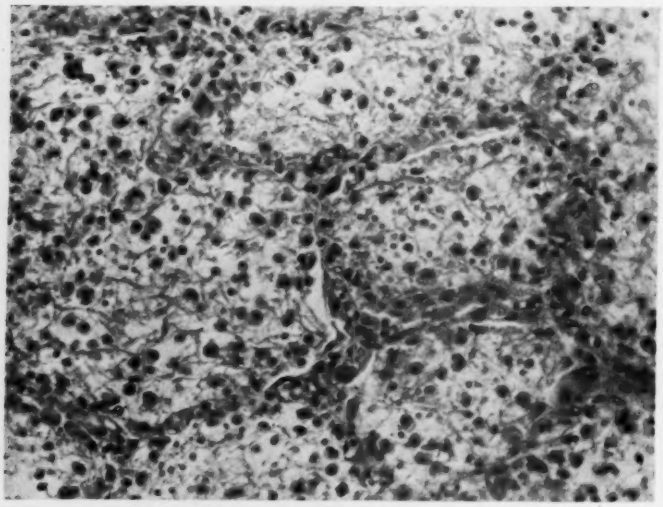

Fig. 2. — Photomicrograph of lung from Case 1, showing alveoli filled with cellular exudate, edema fluid, and fibrin. The leucocytes are predominantly mononuclear. The alveolar septa are edematous.

Fig. 3.—Coronal section through frontal lobes of brain from Case 1, showing multiple small infarcts, principally in the white matter.

exudate, mostly polymorphonuclear, was present in the infarcts adjacent to the occluded vessels.

The kidneys were markedly hyperemic and on microscopic examination showed multiple thrombi of glomerular capillary tufts (Fig. 4).

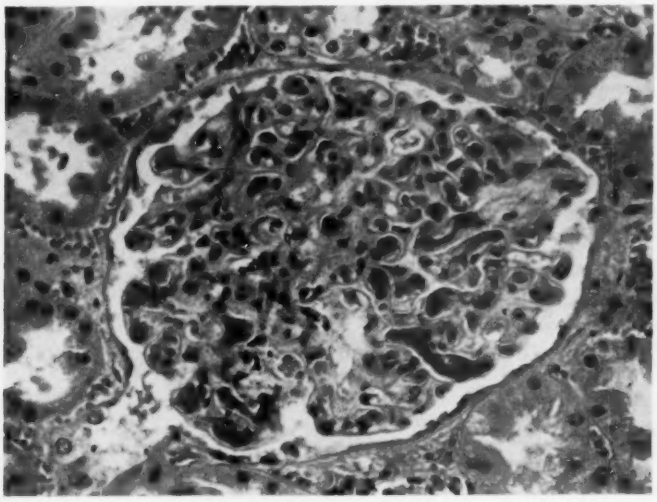

Fig. 4. — Photomicrograph of kidney from Case 1, showing multiple thrombi of glomerular capillary tufts.

The heart showed a single subepicardial hemorrhage, 0.3 cm. in diameter, but was otherwise normal. The spleen was slightly enlarged, weighing 280 gm. and showed hyperemia and reticuloendothelial hyperplasia.

CASE 2.—The wife, aged 37, developed malaise, fever, headache, anorexia, diarrhea, and weakness on the same day her husband, Case 1, became ill. These symptoms increased, and two days later she noted a nonproductive cough, anterior chest soreness, and dyspnea. She had slight myalgia. Although her symptoms were severe, she remained ambulatory through her entire illness in order to care for her husband. She was seen by a physician on the third day of illness and given an injection, following which she improved. She felt entirely well five days after the onset of symptoms, but three days later developed a spontaneous subconjunctival hemorrhage.

CASE 3.—A daughter, aged 16, was in the seventh month of pregnancy. She complained of headache and some malaise on June 13, 1955, the day following the onset of illness in the parents. After a week, she developed fever, sore throat, rhinorrhea, nonproductive cough, and dyspnea. The next day, the cough became productive of small amounts of brownish sputum and coughing caused dull anterior chest pain.

She was admitted to another hospital, in moderate respiratory distress, on June 23, the day her father was hospitalized. Oral temperature was 38.4 C (101.1 F), pulse 112, and blood pressure 70/48. Her pharynx was moderately hyperemic, and a few small anterior cervical lymph nodes were felt. Chest expansion was symmetrical and shallow. There was percussion dullness at both bases posteriorly, with decreased breath sounds and scattered rales. Bronchial breathing and egophony were present at the left base posterolaterally. The uterus was enlarged to an extent consistent with a seven-month pregnancy, and fetal heart sounds were present.

The leucocyte count was 14,500, with a differential count of 42% neutrophiles, 43% band forms, 1% eosinophiles, 13% lymphocytes, and 1% monocytes. The hemoglobin was 9.6 gm. per 100 ml., the hematocrit was 34%, and the erythrocyte sedimentation rate was 59 mm. per hour, corrected to 44 mm. per hour. Urinalysis showed a trace of albumin and many white blood cells and epithelial cells. A repeat leucocyte count four days later was 8000, with a normal differential. Cold hemagglutinins were present in a dilution of 1:80 in serum drawn four days after admission. A sputum culture grew Candida albicans. A chest film showed bilateral lower-lobe pneumonia and elevation of both leaves of the diaphragm.

Treatment for the first day was with penicillin and streptomycin. Therapy was changed to 500 mg. of oxytetracycline every six hours when the diagnosis of psittacosis was suspected. The patient became afebrile within 48 hours, the cough persisted for another 2 days, and she was discharged asymptomatic after 2 weeks of hospitalization. Two months after this illness, the patient was delivered of a normal child at term.

CASE 4.—Another daughter, aged 18, became ill on June 13 with headache, malaise, sore throat, and mild stiffness of the neck. She was unsure of

the character of her illness, but reported that nausea, vomiting, and anorexia, and slight dyspnea developed the next day. She did not have cough or fever, and her entire illness lasted only three days. No antibodies for the psittacosis-lymphogranuloma group of viruses were demonstrated in serum obtained 45 days after onset. This illness can not be confirmed as psittacosis infection.

CASE 5.—A son, aged 10, denied any symptoms suggestive of psittacosis, although he had an antibody titer of 80.

Investigation of Bird Dealer

The two parakeets were purchased at a "dime store," which usually sold from 100 to 150 birds a month. The store obtained birds from a number of sources, both local aviaries and large national dealers. A review of the records of the store showed that the month preceding the purchase of the birds by the family was marked by an unusually high number of bird deaths. During that month 100 birds were received by the store, and 15 died. During the preceding month, 212 birds were received, and 2 died. In the two months following the purchase, the store received 220 birds, and 2 died. In all likelihood, the parakeets purchased by the family were from the group with the unusually high death rate.

Review of the methods used in caring for birds revealed that the salesgirl responsible for bird care added oxytetraycycline to the drinking water of sick birds until they either recovered or died.

At the time of the investigation, the bird section had 15 parakeets. Because two months had passed since the purchase of the two birds given to the family, it is unlikely that any birds of the same lot were left. However, three parakeets were tested, and psittacosis virus was recovered from one.

Blood was obtained from 10 of the store's employees with varying degrees of contact with parakeets. Two salesgirls who handled birds regularly had elevated complement-fixing antibody titers of 20 and 40.

Comment

The case fatality rate in human psittacosis before the introduction of antibiotic therapy was estimated to be approximately 20%.[17] Specific treatment has decreased the rate to about 2%. Fatalities are still limited almost entirely to older patients and those whose care has been neglected, both of which factors were present in the fatal case reported here.

Clinical evidence of infection is unusual in children.[14] In this family of 10 children, the 2 oldest, ages 18 and 16, became ill, but only 1 had laboratory evidence of psittacosis infection. A boy, aged 10, developed a diagnostic antibody titer, although he had no symptoms of psittacosis. This child had cleaned the bird cage on just one occasion, yet his 14-year-old brother who usually cleaned the cage had no symptoms and did not develop antibodies.

Treatment of sick birds with antibiotics in order to make them saleable is a particularly dangerous practice. The addition of antibiotics to drinking water has failed to eliminate infection in a significant number of birds.|| Thus, such treatment converts sick birds to asymptomatic carriers, and they then constitute an ever-present source of human infection in the home.

Attempts to eradicate infection in birds by the use of feed to which antibiotics have been added are in progress. Aviaries can be made infection-free by prolonged use of parenteral antibiotics, preferably tetracycline, but this requires two or three intramuscular injections a day for 14 to 25 days, as well as construction of new cages and other measures to prevent reinfection.[19] It is unlikely that such extensive procedures would be readily adopted by enough aviaries, particularly small local ones, to insure lasting protection for both birds and man.

The increasing number of human cases of psittacosis, although many represent occupational infections traceable to nonpsittacine birds, calls for a reconsideration of control measures, including education of the public and legislation. The most dangerous bird source is still the parakeet in-

|| References 18 and 19.

troduced into the home, and persons who acquire these birds as pets should be informed that seemingly healthy birds may shed virus, bringing sickness, and even death, to the members of their family.

Summary

Four cases of psittacosis ranging in severity from fatality to asymptomatic infection occurred in a family of 12 persons exposed to two apparently healthy parakeets. Psittacosis viruses were isolated from the lung of the fatal case and from one of three parakeets obtained from the same store that sold the original birds.

The increasing number of human infections calls for a reconsideration of the legislation regulating the importation and sale of psittacine birds.

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PROLONGED USE OF ARTERENOL FOR SHOCK FOLLOWING MYOCARDIAL INFARCTION WITH PATIENT SURVIVAL

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SURVEY of the literature, to the best of my knowledge, has not revealed any case of shock following myocardial infarction treated with continuous levarterenol (Levophed) drip for over eight days with patient survival.* It is estimated that the mortality rate is between 80% and 90% [7] in sustained hypotension following myocardial infarction. The delayed gradual onset of shock has been described [8] as the clinical manifestation of progressive failure of the infarcted left ventricle and as almost invariably fatal. This is in contradistinction to the hypotension that may follow immediately after the onset of the infarct, in which case about 50% of the patients recover spontaneously within one hour.

A 52-year-old well-nourished white women developed recurrent episodes of substernal pain of 24 hours' duration. Her husband had died of a brain tumor the preceding day. When first seen at home, she was lying in bed having recurrent attacks of anginal pain which were relieved somewhat by glyceryl trinitrate. She gave a history of similar substernal pains related to exertion which had occurred four years previously. These recurred for about eight months and were treated as a menopausal syndrome by her local physician. Two brothers had died of myocardial infarctions at ages 35 and 49, and a third had suffered two heart attacks by age 60.

The patient was admitted to Weiss Memorial Hospital by ambulance on Oct. 1, 1953, with a diagnosis of angina decubitus with coronary failure and probable premonitary myocardial infarction. She was placed in an oxygen tent and given meperidine (Demerol) as needed, as well as papaverine and pentaerythritol (Peritrate). Blood pressure was 128/80; pulse, 88, and temperature, normal. The lungs were clear on auscultation, and the heart size seemed normal on percussion, although a musical systolic murmur could be heard at the apex. The electrocardiogram showed pronounced U-waves in the precordial leads but no other significant abnormalities.

On Oct. 2, the blood pressure was 120/70; the pulse, 66 and regular; the white cell count, 7500, and the sedimentation rate, 30 mm. per hour (Westergren). There had been no further pain since the midnight following admission. After signing a hospital release against all advice, the patient went to the chapel to attend her husband's funeral, after which she returned to the hospital and reentered her oxygen tent.

Everything went well until the evening of Oct. 3, when her family brought the registry book from the chapel to her room. She became very emotionally upset and cried a great deal. It was at this time that the substernal pain recurred with increasing intensity, unrelieved by glyceryl trinitrate and requiring frequent doses of meperidine and papaverine for relief. By morning the blood pressure had fallen to 86/64, the pulse had risen to 120, and there were basal pulmonary rales and neck vein distention. An apical friction rub could now be heard, and the patient was obviously dyspneic, orthopneic, and slightly cyanotic.

A 1.2 mg. dose of lanatoside C (Cedilanid) was given intravenously, and a 0.2 mg. maintenance dose was given intra-

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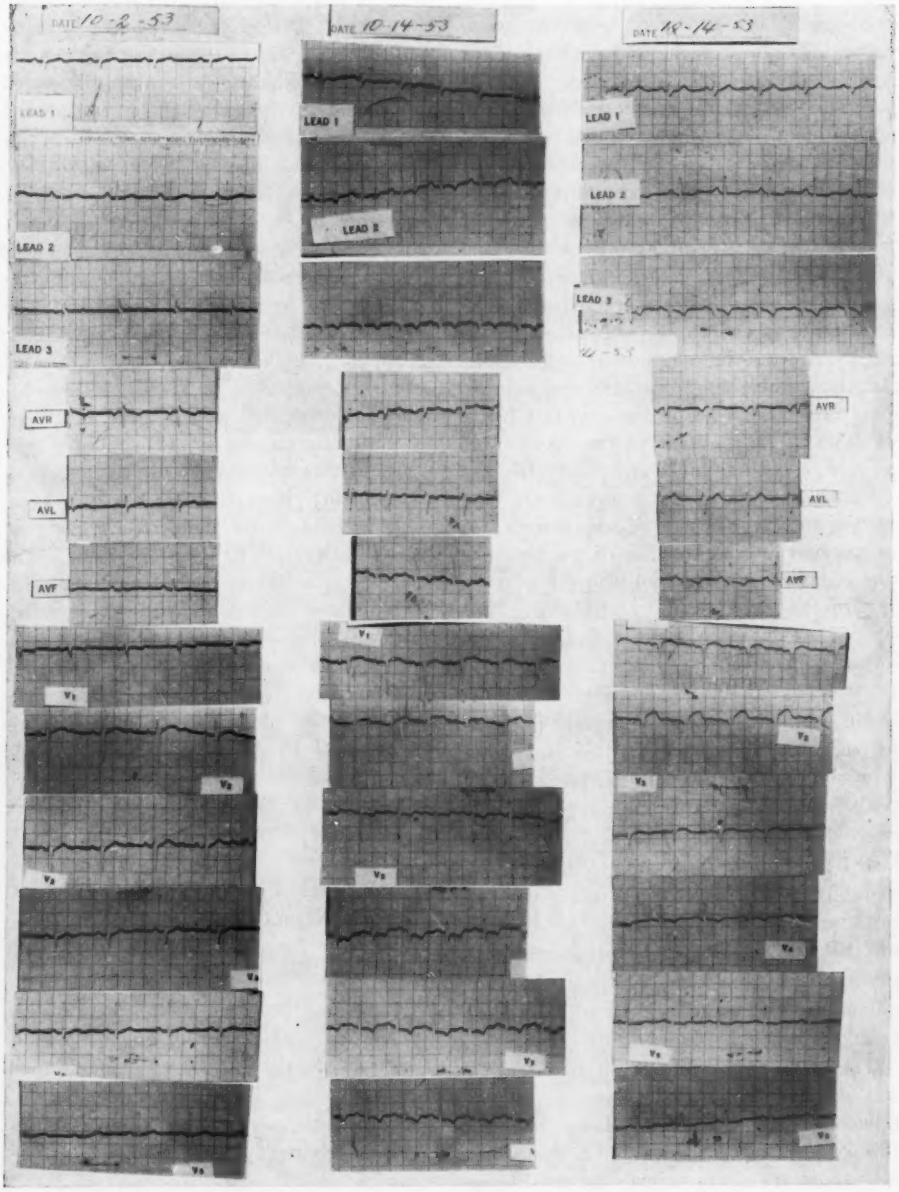

Fig. 1.—On Oct. 2, 1953, note normal R wave in V_2 with prominent U wave in V_{2-5}. On Oct. 14, 1953, note inverted T waves in the three standard leads, aV_F and in V_{2-6}. ST depressions are evident in Lead I and in Leads V_{2-6}. The R wave is now absent in V_2 and is very small in V_3 and V_4. On Dec. 14, 1953, T_1 is again upright, T_2 is diphasic as are the T waves in V_5 and V_6 showing restitution of anterolateral wall ischemia. R wave in V_2 is still absent, and the R wave in V_3 is still very small.

venously daily thereafter. The blood pressure now averaged 96/72. An electrocardiogram revealed recent posterolateral myocardial infarction, with widening of QRS and absent R-wave over the V_2 position, suggesting concomitant septal involvement. Whenever the pressure dropped below 90 systolic for over 15 minutes, 15 mg. of mephentermine was given intramuscularly and repeated at two-hour intervals in an effort to keep the blood pressure above 90 mm. of Hg systolic.

On October 10, one week after the infarction was definite, it was necessary to start arterenol by continuous intravenous drip, since her blood pressure now ran between 60/50 and 74/58 for over two hours in spite of intermittent vasopressors. Her skin was cool and clammy, and she was cyanotic in spite of the oxygen tent. The administration of 500 cc. of plasma resulted only in accentuation of the pulmonary edema. The arterenol was given as 16 mg. of the bitartrate (Levophed) in a liter of 5% dextrose in water. The flow was adjusted in an effort to maintain a systolic pressure of 90-100 mm. of Hg.

On the night of Oct. 11, severe pulmonary edema with loss of pulses and coma necessitated the use of tourniquets and positive-expiratory-pressure oxygen to tide over the acute left heart failure, which lasted six hours. One cubic centimeter of meralluride (Mercuhydrin) was given intramuscularly and daily thereafter because of the marked dyspnea, orthopnea, pulmonary rales, and x-ray evidence of severe pulmonary congestion with marked cardiac enlargement.

The total eosinophile count on Oct. 13 was 460 per cubic millimeter. Fritz and Levine[10] demonstrated in 1950 that the adrenal steroids act locally on the small splanchnic vessels in animals by sensitizing them to the action of arterenol. Kurland and Freedberg,[9] in 1951, reported their studies on the potentiating effect of steroid therapy on the pressor response to levarterenol in humans. With these facts in mind, intravenous and intramuscular cortisone were given from Oct. 13 to 20. After the initial 100 mg. was given slowly intravenously 25 mg. was given intramuscularly daily. This was prior to the advent of intravenous hydrocortisone, but no adverse effects were apparent from the use of the cortisone intravenously. Fluid intake was kept between 1500 and 2000 cc. daily in an effort to avoid overloading the myocardium. Because of a low chloride level (84 mEq. per liter) associated with the hypotension, sodium, potassium, and ammonium chlorides were used as seemed indicated. Antibiotics were used to combat a left pneumonitis, and the prothrombin time was controlled with as little as 25 mg. of bishydroxycoumarin (Dicumarol) per week. It was necessary to use phytonadione (Mephyton) intravenously on two occasions because of the dangerously low prothrombin levels (10% of normal). The response to a 100 mg. dose was poor. This phytonadione-resistant hypoprothrombinemia was possibly related to the liver ischemia plus the antibiotic effect on the intestinal flora. Liver function tests were not markedly abnormal, but the palmar erythema of so-called "liver palms" could be identified. Recheck of liver function tests including the prothrombin time six months later revealed normal values.

Levarterenol, which had been given around the clock since Oct. 10, was gradually reduced on Oct. 23 and finally stopped on Oct. 24, fourteen days after the onset of the continuous sympathicomimetic stimulation. During this time a total of 402 mg. of arterenol had been given.

On Oct. 26, there occurred a temperature elevation to 106 F, without chills but associated with an erythema-nodosum-like rash. A remittent spiking fever to 104 F recurred daily. There was no associated leucocytosis, and blood cultures were negative. At this point, the blood pressure again dropped to 72/40, and when the patient refused any further intravenous therapy, intramuscular phenylephrine (Neo-

Synephrine) was started, 10 mg. every one to two hours, in order to maintain the systolic pressure at 90 or over. On analyzing the temperature chart, it was noted that there was an apparent close association between the mercurial injection and the daily spike in fever, so the meralluride was stopped in an effort to exclude a drug fever. The febrile course subsided following cessation of mercurial therapy. However, because the pulmonary edema could not be controlled with low sodium intake, digitalis, and xanthine diuretics, it was necessary to start mercaptomerin (Thiomerin) hypodermically in gradually increasing doses. The diuretic response was adequate, and drug fever did not recur. Thereafter recovery was slow but in a steadily upward course.

The patient was removed from oxygen after two months and was gradually mobilized after three months. Digitalis was stopped after six months, and she has required no mercurial diuretics since leaving the hospital. She has been maintained on pentaerythritol and a low-fat diet, the latter because of a moderate hypercholesterolemia on several rechecks. Chest roentgenograms have shown complete clearing of the lungs and a decrease in heart size to practically normal limits. Anginal attacks are a rare occurence, and the patient is living a normal life at this time, over two years after the original infarction.

This case is being reported with a two-year follow-up because it exemplifies several interesting observations. Emotional trauma appeared to precipitate a severe myocardial infarction at a time when the status anginosus seemed relatively well controlled. The gradually progressive shock-like picture with heart failure was reversed after 14 days of continuous sympathomimetic stimulation with arterenol along with seven days of corticosteroid therapy. The author feels that the difference between failure and success in treating shock rests with early treatment before irreversible changes occur. This requires close observation of the patient and switching from frequent intramuscular injections of vasoconstrictors to continuous intravenous arterenol drip, which its greater ease of pressure control, as soon as one finds it impossible to maintain an adequate blood pressure by intermittent therapy. It is not an unusual occurrence to see a patient with cardiogenic hypotension develop convulsions and die from cerebral anoxia before the typical picture of peripheral vascular collapse occurs.

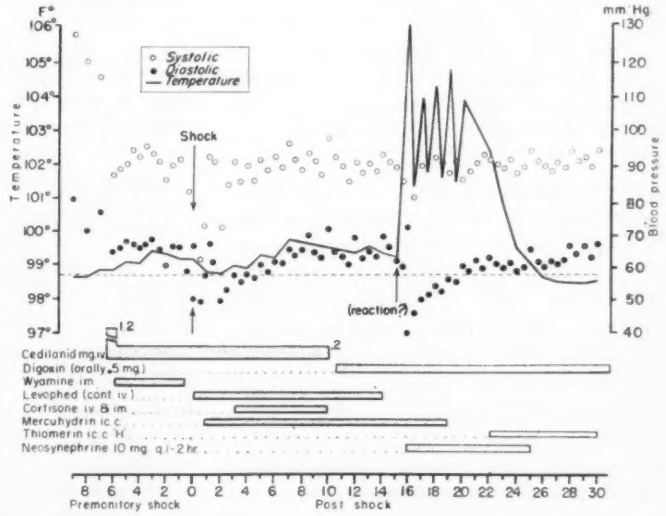

Fig. 2.—Summary of clinical course and medication used. Note length of time meralluride was used before suspected febrile hypersensitivity reaction occurred.

Since arterenol apparently does not increase myocardial irritability, it may be that earlier use of this potent vasoconstrictor before frank evidence of vascular collapse sets in might increase the salvage rate in severe hypotension associated with myocardial infarction. As it is impossible to tell which patient's hypotension will spontaneously reverse without therapy, it might be that some would be treated needlessly. On the other hand, by waiting one to two hours before starting intravenous vasoconstrictors, valuable time may be lost in those who will require such care. The length of treatment would be relatively short in the former group. Decrease in urinary output may be used as an indicator for strenuous antishock therapy in borderline cases of clinical shock. Constant care to see that the levarterenol solution does not escape from the vein is necessary. However, skin sloughs caused by infiltration will usually heal without grafting after a period of several months.

Drug fever apparently resulted from meralluride administration over a 16-day period. No fever resulted when another mercurial was used. And finally, hope for an ultimate excellent clinical recovery should not be despaired of because of the marked evidence of prolonged cardiac failure following acute myocardial infarction. That a pessimistic attitude is not justified is evident from the follow-up of this case. After six months, heart size had returned virtually to normal and the lungs were completely cleared. Two years later, the patient leads a normal existence, with only a rare anginal attack precipitated by emotional upsets or by walking in the cold weather against a strong wind.

Conclusions

The preceding case report exemplifies the excellent recovery of a patient following myocardial infarction with prolonged shock treated with levarterenol by continuous intravenous drip for fourteen days along with parenteral cortisone for seven days.

55 E. Washington (2).

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HEMORRHAGIC THROMBOCYTHEMIA
A Blood Coagulation Disorder

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AS WOULD BE anticipated, disorders with moderately increased blood platelet levels are often characterized by thrombotic complications. Paradoxically, massive increases in the platelet count are more frequently associated with a hemorrhagic disorder.[1] Thus, such diseases as polycythemia vera, chronic granulocytic leukemia, and essential thrombocythemia may present a hemophilia-like syndrome when the platelets exceed a million per cubic millimeter. The mechanism by which thrombocythemia leads to bleeding has been the subject of much speculation, but few of the suggested theories have been implemented by experimental verification. The present study concerns a case of thrombocythemia resulting from polycythemia vera. Data to be presented indicate that excess platelets display anticoagulant activity. Both thrombocythemic and normal platelets were found to be similarly anticoagulant at comparable concentrations. The findings suggest that the platelet anticoagulant effect may be at least partially responsible for the hemorrhagic manifestations of thrombocythemia.

Report of Case

A 71-year-old woman was first admitted to Montefiore Hospital in July, 1950. The presenting findings at that time were those of serum hepatitis. For the preceding 15 months there had been recurrent episodes of tarry stools, and a roentgenological diagnosis of peptic ulcer had been made. On several occasions whole-blood transfusions were administered because of severe anemia, the most recent having been given one month prior to admission. Shortly thereafter the patient developed nausea, anorexia, and vomiting, which was accompanied by pruritis, jaundice, dark urine, and light stools. No relevant findings were obtained from the past or family history.

Physical examination revealed a moderately ill, aged woman who was poorly nourished and quite icteric. The liver edge was palpated about 7 cm. below the right costal margin, but no splenomegaly was reported. The remainder of the examination showed no significant abnormal findings.

Pertinent laboratory findings were as follows: Routine urine examination was negative. The serum bilirubin was 14.3 mg. per 100 cc., and the thymol turbidity was 11 units; however, the alkaline phosphatase and cephalin flocculation tests were within normal limits. X-ray studies of the gastrointestinal tract showed a deformed duodenal bulb without definite evidence of crater formation; the barium enema failed to demonstrate any lower intestinal abnormality. The hematological data are summarized in Figure 1. These included a moderate hypochromic, microcytic anemia; leucocytosis with an essentially normal differential count, and an appreciable increase in platelets. The bone marrow showed megakaryocytic hyperplasia.

After hospitalization the symptoms and laboratory abnormalities of hepatitis gradually disappeared. However, five days after admission the patient had an episode of massive gastrointestinal bleeding which necessitated the use of blood transfusions. After a month of hospitalization the patient was discharged considerably improved, only to be readmitted one week later because of a massive hematoma on the right side, extending from the hip to the shoulder. This lesion developed without any definite history of trauma. In the subsequent five-year period the course was characterized by repeated episodes of gastrointestinal bleeding, many of which were treated with blood transfusions. In all, 16 such episodes were recorded. Two 1000 r courses of x-ray therapy were given to the gastric area in an attempt to reduce gastric acidity—one in June and the other in December, 1951. In February, 1953, whole body radiation, 35 r, was given to depress the blood platelets. For almost two years following this treatment the patient appeared to be relatively free of hemorrhage.

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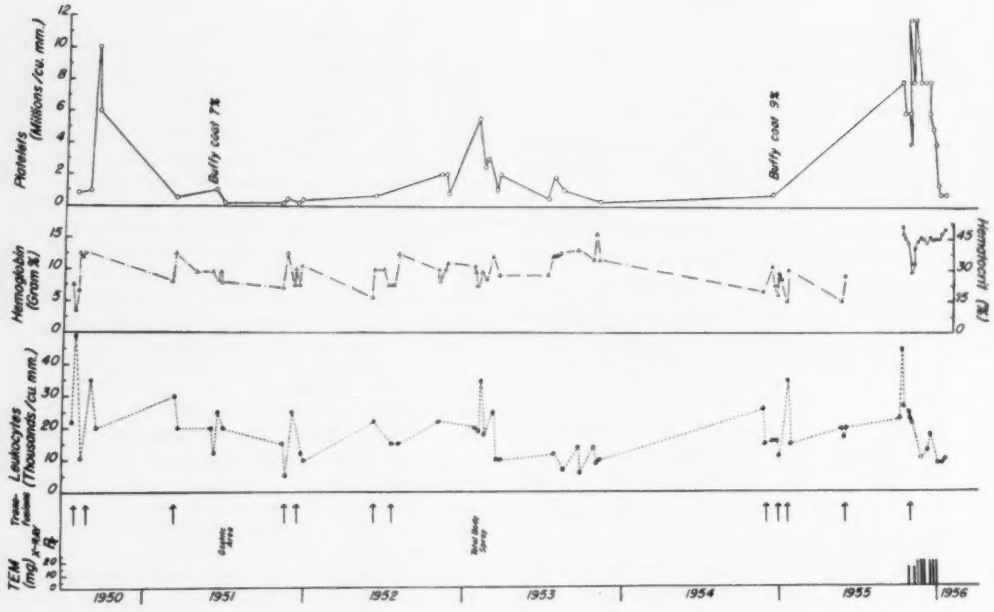

Fig. 1.—Hematological summary of reported case. The platelets were probably underestimated in earlier studies, as evidenced by the discrepancy between counts and buffy coat.

and lower platelet levels were recorded. Aside from this period, the course was characterized by a persistent elevation of blood leucocytes and generally an increase in platelets that was often massive. The erythrocytes varied between anemic and slightly polycythemic levels, depending on the frequency and severity of blood loss (Fig. 1). In 1953, a series of coagulation studies was performed. At that time, the blood coagulation time, prothrombin, prothrombin consumption, fibrinogen, and clot retraction were all normal. The heparin clotting time was found to be definitely shortened.* The patient was carried with a clinical diagnosis of polycythemia vera.

In addition to her hematological problems, the patient began having symptoms of congestive heart failure in 1951 and several times presented the findings of pulmonary edema. Moreover, in 1953, she had an attack of gouty arthritis in the right great toe.

The most recent admission dated from Oct. 13, 1955, at which time the patient presented with a massive, spontaneous epistaxis. The physical findings were essentially unchanged, except that splenomegaly to just below the costal margin was first detected. The hematological picture was as before. A repeat bone marrow aspiration showed a mark-

* These studies were performed by Dr. Robert Rosenthal.

edly hypercellular specimen. Erythroid precursors were increased to a greater degree than neutrophiles, but most striking was a dramatic proliferation of active megakaryocytes, as shown in Figure 2. The bone marrow picture was that of polycythemia vera. An additional laboratory finding of note was a serum uric acid value elevated to 8.1 mg. per 100 cc.

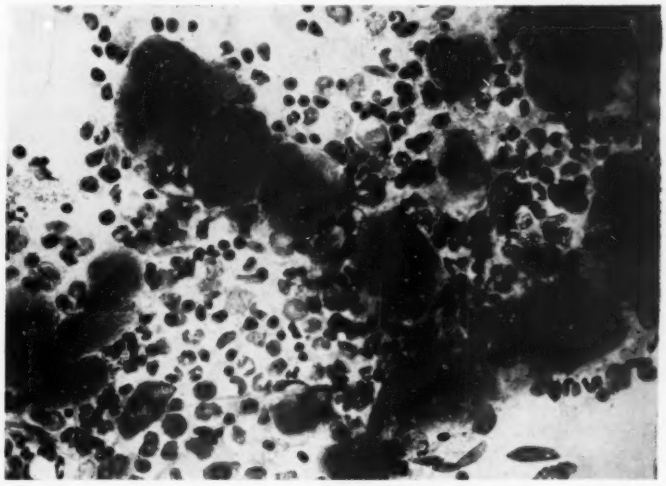

Fig. 2.—Bone marrow aspiration in reported case.

On Oct. 30, 1955, the patient was started on repeated courses of therapy with triethylene melamine (TEM), as indicated in Figure 1. As can be seen, she was quite resistant to this drug and even on massive doses responded with an incomplete restoration of platelets toward normal levels. The leucocytes were similarly affected, but the erythrocyte picture was complicated by severe gastrointestinal bleeding for several days, starting on Nov. 2. Jan. 2, 1956, the patient accidentally fell, suffering a minor scalp injury. A large ecchymotic area in the facial and frontal regions resulted. The remainder of the course was otherwise uncomplicated by hemorrhagic manifestations.

Blood Coagulation Studies

Methods.—Whole-blood coagulation times were determined by the Lee-White method. Plasma prothrombin determinations were accomplished both by the Quick [2] and by the Ware and Stragnell [3] techniques. Labile factor was measured as described by Quick,[2] and serum prothrombin as by Ware and Stragnell.[3] Fibrinogen was estimated turbidimetrically by the method of Fowell.[4] The thromboplastin generation test was modified from the original method of Biggs and Douglas,[5] as described elsewhere.[6] Plasma was obtained from blood collected in one-tenth volume of either 0.1 M potassium oxalate or 3.8% sodium citrate, as indicated. All coagulation studies were performed in a 37 C water bath.

Results.—When these studies were performed,

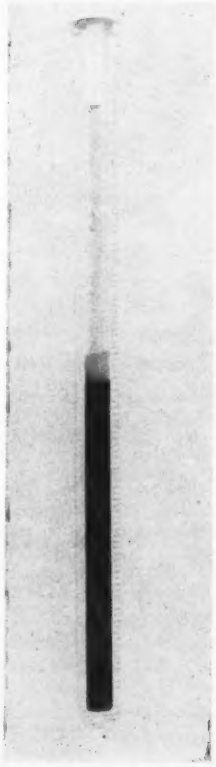

Fig. 3.—Hematocrit in reported case.

the patient's platelets numbered approximately 10,000,000 per cubic millimeter. This massive increase in platelets was reflected in the length of the buffy coat obtained when the hematocrit was determined. In Figure 3 it can be seen that the "thrombocytocrit" is over 5%, whereas normally it is too small to estimate.

The Table shows the results of the patient's routine blood coagulation studies. These were within normal limits except for a somewhat prolonged prothrombin time by the Quick method. This prolongation appeared to result from a slight decrease in labile factor.

Routine Coagulation Studies in Reported Case

Coagulation time (Lee-White)	12 min.
Clot retraction	Normal
Rumpel-Leede test	Negative
Skin bleeding time (Duke)	4 min.
Prothrombin (Quick)	80%
Prothrombin (Ware & Stragnell)	90%
Labile factor (Quick)	60%
Serum prothrombin (Ware & Stragnell)	6%
Plasma fibrinogen	770 mg./100 cc.

Figure 4 shows the results of the thromboplastin generation test. When the test was performed using only the patient's reagents, there was marked retardation of thromboplastin generation. The test became normal when normal platelet reagent or brain lipid[7] was used in place of the patient's platelet reagent. Moreover, use of the patient's platelet reagent together with normal serum and plasma reagents produced an abnormal thromboplastin generation curve identical to that obtained in the original test with all reagents derived from the patient's blood. These findings incriminated the patient's platelet reagent as being responsible for her faulty thromboplastin generation.

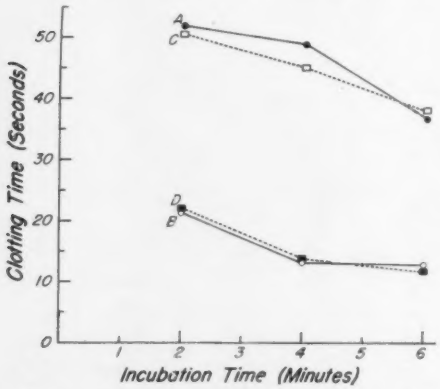

Fig. 4.—Thromboplastin generation curves with various platelet suspensions. *A*, Platelets in reported case, concentration 10,000,000 per cubic millimeter. *B*, platelets in reported case, concentration 1,000,000 per cubic millimeter. *C*, normal platelets, concentration 10,000,000 per cubic millimeter. *D*, normal platelets, concentration 1,000,000 per cubic millimeter.

The patient's platelet reagent contained about 10,000,000 platelets per cubic millimeter. When these platelets were subjected to dilution in isotonic saline, they became progressively more effective in the thromboplastin generation test as the concentration decreased until, at a level of about 1 million per cubic millimeter, they gave a normal curve (Fig. 4). It was therefore concluded that the platelets had produced an abnormal thromboplastin generation curve as a result of their excessive concentration, rather than having some qualitative defect. This conclusion is in conformity with the finding that the patient's blood showed normal clot retraction and prothrombin consumption.

The following additional studies confirmed that the patient's platelets behaved normally: Platelet-poor normal plasma was obtained by centrifuging normal citrated blood for one hour at 3000 rpm. Aliquots of 0.9 cc. were pipetted into each of three Kahn tubes. Into the first of these was pipetted 0.1 cc. of the patient's platelets diluted to a concentration of about 1,000,000 per cubic millimeter. To the second was added 0.1 cc. of normal platelets of the same concentration, and to the last was added 0.1 cc. of isotonic saline. Each specimen was then recalcified with 0.1 cc. of 0.1 M calcium chloride solution, and all were incubated for one hour at 37 C. Clot retraction was found to be complete in both specimens containing platelets but was absent in the saline control. In a second experiment, 0.1 cc. of the patient's platelets was added to 1.9 cc. of blood from a patient with thrombocytopenic purpura whose platelets numbered 20,000 per cubic millimeter. To an additional 1.9 cc. aliquot of this same blood specimen was added 0.1 cc. of isotonic saline. Serum prothrombin was measured after two hours of incubation at 37 C. The following results were obtained: Serum prothrombin with patient's platelets added—under 1%; serum prothrombin with saline added—48%. Thus, the patient's platelets elicit normal prothrombin consumption and clot retraction in other blood as well as in their native blood.

The behavior of highly concentrated normal platelets was studied. A 250 cc. volume of normal blood was collected in citrate, and the platelets obtained from this specimen were suspended in 1 cc. of saline, giving a count of about 10,000,000 per cubic millimeter. These platelets were studied in the thromboplastin generation test. As shown in Figure 4, the concentrated platelets produced an abnormal curve, but dilution to a level of 1,000,000 per cubic millimeter restored normal activity. The normal platelets were similar to those of the thrombocythemic patient in being anticoagulant when excessively concentrated.

These data indicate that an excess of platelets exerts an anticoagulant effect in the thromboplastin generation test, and presumably this effect has a parallel in vivo inhibition of blood coagulation. At present it is not possible to determine whether the anticoagulant arises from superoptimal concentration of a single coagulant material or whether the platelets contain a separate inhibitory agent whose action becomes evident only at high concentrations.

Comment

The association of a hemorrhagic disorder with high blood platelet counts has been amply documented. Attention was first brought to this problem in 1920, when di Guglielmo† reported a case of "piastrinemia" characterized by erythremia, leucocytosis, and greatly increased platelets and megakaryocytes in the blood. Despite the thrombocythemia, the patient had a bleeding tendency. This same author also described hemorrhagic manifestations in patients whose platelets were elevated in the course of chronic granulocytic leukemia. Since that time numerous reports have appeared confirming the association of thrombocythemia and bleeding in patients with chronic granulocytic leukemia, polycythemia vera, and "essential thrombocythemia."‡ In addition, a few patients have been described whose thrombocythemia followed splenectomy and who presented both thrombotic and hemorrhagic manifestations.[12]

Suggested hypotheses as to the pathogenesis of bleeding in thrombocythemia fall into four general groups: 1. That the bleeding is vascular in origin. Proponents of this viewpoint are divided between those who favor a general increase in vascular fragility[15] and others who feel that thrombotic lesions cause local vascular damage.[24] There is little evidence to support the vascular hypothesis and much against it. As pointed out by Minot and Buckman§ the bleeding in thrombocythemia is clinically that of a coagulation disorder rather than that of a vascular problem. Instead of developing "spontaneous" petechiaé and ecchymoses of the skin and mucous membranes, the patients characteristically bleed only in response to trauma. Moreover, the tests for capillary fragility are usually negative, as in the present patient. 2. That there is an intrinsic platelet defect. Early investigators impressed by morphological abnormalities of the platelets suggested that in the face of thrombocythemia the platelets themselves were somehow defective.[13] Certain experimental findings appear to lend credence to this hypothesis. Bigelow[27] reported that the blood serotonin content was subnormal in patients with thrombocythemia. As serotonin is derived from platelets, this would appear to incriminate these cells as failing to supply the vasoconstrictor agent. Most recently, Hardisty and Wolff[28] studied thrombocythemic platelets in the thromboplastin generation test. They diluted thrombocythemic platelets to normal concentrations and reported reduced activity; but normal tests resulted when the platelets were used in somewhat greater concentration. The results of these authors are open to the critisism that the differences between thrombocythemic and normal platelets were not great. Indeed, the differences obtained are not statistically significant. It is difficult in any case to accept the concept that mild, qualitative platelet defects could be responsible for a hemorrhagic disorder where there is a huge platelet increase that should more than compensate for any partial deficiency. Actually, the severity of bleeding appears to be proportional to the degree of platelet increase. Moreover, transfusions of platelets from patients with thrombocythemia improve the hemorrhagic tendency of patients with thrombocytopenic purpura at least as well as do transfusions of platelets from normal donors.[1] It is therefore probable that thrombocythemic platelets are functionally normal, or at least effective hemostatic agents. 3. That there is a coagulation disorder which accompanies thrombocythemia but involves other clotting factors. Hypofibrinogenemia has been re-

† References 8 and 9.
‡ References 10-26.
§ References 10 and 11.

ported in patients with thrombocythemia, especially in those whose underlying disease is polycythemia vera.[1] However, the depression of fibrinogen is generally not sufficient to account for a hemorrhagic disorder, and it is by no means universal among thrombocythemics. A recent study by Levin, Celander, and Guest [29] attempts to implicate combined prothrombin and fibrinogen deficiency in a single patient. According to these authors, the sequence of events leading to hemorrhage was as follows: Subclinical thrombosis led to the liberation of excess platelet coagulants causing in vivo utilization of prothrombin and fibrinogen, with temporary depletion of these factors. Although many factors may augment the hemorrhagic tendency of certain patients with thrombocythemia, at present the only established common denominator is the increase in platelets.

The present studies suggest, 4., that the anticoagulant effect of excess platelets produces a blood coagulation disorder. Anticoagulant activity in platelets has been previously described. In 1936, Chargaff and associates [30] showed that the defatted residue of horse platelets prolonged the recalcified clotting time of chicken plasma. Tocantins and Carroll [31] extensively studied a lipid anticoagulant widely distributed throughout all tissues which was capable of interfering with the action of tissue thromboplastin. Our own data correspond closely to those of Klein and Farber ‖ and show that highly concentrated platelets can be anticoagulant in human coagulation systems. Independent observations from both laboratories have demonstrated interference with thromboplastin generation when the platelet level is increased to levels of about 2,000,000 per cubic millimeter and over. Thus, anticoagulant concentrations of platelets are well within the range encountered clinically in patients with thrombocythemia. Additional findings to be published elsewhere are also in agreement with those of Klein and Farber ¶ and show that the platelet anticoagulant has a dual action: it interferes with blood thromboplastin formation, and it inhibits the action of thromboplastin already formed.

It is reasonable to assume that excess platelets can exert an in vivo anticoagulant effect comparable to that encountered in the thromboplastin generation test. It is therefore likely that the hemorrhagic manifestations of thrombocythemia are at least in part related to the platelet anticoagulant. In this respect, hemorrhagic thrombocythemia is another disorder in which a circulating anticoagulant interferes with the first stage of blood coagulation.

Summary

A case of hemorrhagic thrombocythemia is reported. The patient had platelet counts reaching 10,000,000 per cubic millimeter and presented a variety of hemorrhagic manifestations. Her platelets displayed anticoagulant activity in the thromboplastin generation test when used at circulating levels but behaved normally when they were diluted to normal levels. Normal platelets were similarly anticoagulant when concentrated to thrombocythemic concentrations. It is suggested that the fundamental defect in hemorrhagic thrombocythemia is a coagulation disorder resulting from the anticoagulant effect of excess platelets.

Addendum

The patient's subsequent course has been as follows: By March, 1956, the platelet count had again risen to about 2,000,000 per cubic millimeter and the hematocrit was up to 58%. At this time 4 mc. of P_{32} was given by the intravenous route. In addition, 500 ml. of blood was removed by venesection. Within a month the platelets had fallen to normal levels, where they have remained to this date (June 20, 1956). The hematocrit has likewise been normal. No further hemorrhagic episodes have occurred.

‖ Klein, E., and Farber, S.: Personal communication to the authors.

¶ Klein, E., and Farber, S.: Personal communication to the authors.

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Books

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BOOK REVIEWS

High Blood Pressure. By George White Pickering, M.A., M.B., M.D. Price, $9.50. Pp. 547. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

It is hard to review a book like Pickering's superb monograph on high blood pressure without praise becoming fullsome and a little cloying. It is only within the past few years that I have broken myself of reading every word in a book. This capacity was wasted here since this monograph is impossible to skip around in. The level of interest is always high. The style is a most excellent example of the simplicity, directness, and clarity that the diminishing band of American physicians who still read expect from their British medical brothers. Still, this good book is seasoned by a few peppery comments. The occasional rapier thrust suggests that the style has been tempered by conscious and conscientious restraints. The unexpected turn, the light touch of fancy, make it an easy book to read.

The title of the book is arresting; it gives the first inkling of the general theme. That theme is to consider the problem of blood pressure in terms of the experience of the world at large. What is the distribution curve of blood pressure levels in an extensive population? The title suggests that critical judgment has found in high blood pressure an exaggerated physiological state rather than a "disease." The problem is whether high blood pressure represents a disease or the upper part of a normal distribution curve. For comparison, consider the problem of height and weight. Very great extremes in height do in fact occasionally represent the result of stimuli which make gigantism a disease; but well within the range of the same curve where hypertension falls on a blood pressure distribution curve, tallness would not be construed as a disease. On the other hand, with obesity the differentiation between disease and health may be a closer one. But here again the matter of dialectics and semantics makes mincemeat of critical thought. We ultimately ask the question whether obesity is a disease or brings as inevitable concomitants certain disorders or diseases. These are not idle points but are critical to every problem in clinical medicine. For nowhere is confusion greater than in the field of inquiry into the nature of the processes and meaning of disease. Just as pain may be looked upon as having a certain personality or quiddity, being personified as something evil which invades the body, so disease may be looked upon as something evil which assails the body from without or arises from within instead of being the processes of reacting to stimuli.

In this book on high blood pressure, the distinction between facts, hypotheses, and words is clearly established and kept in view. This reminds us of the cruel fact that one of the miracles of modern science in improving the health of patients at large has been at times the mere discovery that a disease does not exist. Take for example the spectacular invention of visceroptosis, when x-rays suddenly revealed to the inquisitive radiologist the natural effects of gravity on the alimentary canal. Much later came the slow realization that visceroptosis was not to be attacked by corsets and exercises but to be accepted as one of the simple hazards man met when he undertook the erect posture.

Those exercised by priority who feel urged to hurry things half done into print may be interested to realize that Pickering tried adrenalectomy without any flourish of frumpets or loud noise considerably before the present vogue was introduced. It is of interest also that he gave up the procedure as relatively futile.

Pickering's book is the scholarly distillate of a productive life in clinical investigation and clinical thought. From his own extensive investigation and the published reports of his colleagues all over the world he uses vast bodies of data selectively to illustrate the approach to simplification which may be reached by the hard road of complexity. While his conclusion that essential hypertension is but a portion of a distribution curve may make a nervous wreck of certain rigid proponents of this or that special idea of pathogenesis, the gain we can expect from a stimulating reappraisal is well worth the effort.

Dr. Pickering has been in the forefront of advance in clinical research upon the problem of blood pressure. From the early days of his association with Sir Thomas Lewis, his con-

tributions to medical writings have been distinguished for their critical approach and imaginative concern with the problems of blood pressure, blood vessels, and circulation. These problems are not minor. I should like to quote something I said elsewhere about the topic of blood pressure: "Worship of science has a very baleful effect on the frights and fears of an already neurotic population. That instrument of woe, the sphygmometer, links much of the populace in conspiracy with the medical profession in the clinical numbers racket. Figures are banded around with a glib assurance that they have some meaning and truth rather than as the paraphernalia of an artificially engendered neurosis. We have a vast lay public, scientifically unequipped to comprehend or even guess the significance of the numbers and yet they may employ them as a skeleton of their framework of hypochondriasis. The authoritarian but frequently changed pronouncements of self appointed boards of authority on normal blood pressure disclose that this too is a figment. The most we can say is that there are normal blood pressures rather than a normal blood pressure."

With the established and recognized causes of hypertension, Pickering has no argument. Pheochromocytomas, primary renal disease of various kinds, Cushing's syndrome, coarctation, and polyarteritis nodosa are discussed with insight and illumination along accepted lines of orthodoxy. But his new concept is that the "differences between so-called normal subjects and those with essential hypertension are quantitative." For that reason, Pickering and his co-workers make the decision to "stop pursuing the futile search for the dividing line between normality and hypertension . . . . any such attempts are merely attempts to create artefacts with all the confusion that ensues on the acceptance of an artefact as a real phenomenon. Again, the division of the early course of essential hypertension into stages of pre-hypertension, latent hypertension, and fixed hypertension is regarded as a secondary artefact consequent on the first; the classification, moreover, that imperfectly describes diurnal and other variability and the effects of age."

Recognizing this as at least an acceptable hypothesis, how to manage patients whose blood pressure is at the far end of a distribution curve, whether qualitatively abnormal or only having too much blood pressure, proposes the usual problems of identification, clinical evaluation, and management. The confusing and vexing problems of the present day desalting, antihypertension regimens are dealt with effectively, critically, and with insight. This book will add further renown to its distinguished author. It will serve as a soothing and informative essay for some. For others it will provide the upsetting necessity of checking their concepts. For all who study its meaning, "High Blood Pressure" will be a challenging approach to a problem about which we all need clearer understanding. Equally important, it is excellent food for contemplation for those who desire to think about sickness and health as well as to treat reflexly and automatically with the latest gadget or magic pill of our era of pushbutton therapy any person deviating from "the normal."

WILLIAM B. BEAN, M.D.

1955 Medical Progress: A Review of Medical Advances During 1954. Edited by Morris Fishbein, M.D. Price, $5. Pp. 322. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36, 1955.

A review of medical advances during 1954 is presented in "1955 Medical Progress," the third in a series of volumes. This is done by recapitulating in a brief, simple, and yet authoritative and comprehensive manner the progress of the year in numerous fields of medicine.

In each topic discussed, and there are many, enough background is given to provide sufficient orientation from which to progress. This is especially valuable when realizing that discoveries are not usually made at a certain moment but rather through a period of time which may vary.

To give a brief idea of what one might encounter in this book, a few topics are mentioned. In the field of pharmacology, Diamox, chlorpromazine, Rauwolfia serpentina, and *d*-lysergic acid diethylamide are given with their latest uses and actions described.

Physical medicine provides an interesting contribution to the bedridden patient for the prevention of decubitus ulcers. This consists of an alternating air-pressure pad (a pneumatic mattress) placed on top of the usual bed mattress. Rows of air cells are filled and emptied alternately every three minutes by an electric pump. The patient is unaware of these changes, and the results are rewarding.

It has been shown that deficiency in pyridoxine (vitamin B_6) can give rise to symptoms such as anorexia, confusion, seborrheic dermatitis, and inflammation of the tongue. Uncontrolled absorption of iron without utilization has also been related to the deficiency of this vitamin.

A new x-ray technique is practiced in an ultrasonic photographing instrument to give views of internal tissues and soft organs. This device is called the "Somascope" and combines television, sonar, and radar. A brief description of the procedure is included in the progress note.

For the busy physician who wishes to have a "nutshell" review of the discoveries in the medical profession over the last year's period of time, this book has very much to offer.

ANNA KATHERINE KNAPP, M.D.

Exogen Faktoren in der Pathogenese der Poliomyelitis (erlæutert an dem Ergebnis von Untersuchungen wæhrend und nach der Epidemie in Nordrheim-Westfalen. By Dr. R. Ch. Behrend. Price, $3.40. Pp. 98, with tables and charts. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1955.

In this monograph Dr. Behrend has compiled the data from a very competent and thorough study of an epidemic of poliomyelitis which occured in Nordheim-Westfalen, Germany, in 1952. Particular emphasis is placed upon a consideration of the exogenous factors which the author and many other authorities in the field feel predispose a person to clinical poliomyelitis. Among the possible factors considered are sex, age, occupation, general body heredity, sports activity, travel, injuries, fractures, contusions, burns, skin injuries, and concusion. Inflammatory processes, such as furuncles, otitis, and insect bites, are also considered. Another section deals with the possible effects of operative procedures, such as appendectomy, herniotomy, dental operations, tonsillectomies, vaccinations, and injections. The possible effect of climate and chronic illness is also covered.

One of the interesting facts which was brought to light in this study was the relatively high incidence of paralytic poliomyelitis among the heavy manual laborers of the area.

Since the authors have included a complete bibliography, this book would be helpful to persons interested in the epidemiology of poliomyelitis, but it does not offer any new concepts of transmission or predisposition.

HARRY HARDING, M.D.

A Devotion to Nutrition. By Frederick Hoelzel. Price, $2.50. Pp. 88, with no illustrations. Vantage Press, Inc., 120 W. 31st St., New York 1, 1954.

This a chatty little book by one who has obviously devoted a large share of his life to introspecting and speculating about the function of his alimentary canal in terms of fitness, subjective sensations, and the like. Hoelzel's work as a subject in Carlson's laboratories adds a note of historic interest. It is an intensely personal document by one who approaches scientific problems with the enthusiasm of a zealot rather than the objectivity of a critical and skeptical student. One of the major features is the large number of historic allusions to food fads and faddists of fifty years ago. In the realm of science nothing has given rise to so much speculation as food and nutrition. It has been largely neglected by clinical investigators for so long it is not surprising that such an important area has been invaded by the enthusiast and the crackpot.

This book will not satisfy the rigid criteria of a scientific document. It is very well named in the title "A Devotion to Nutrition." The main emphasis is on the possibility of advancing knowledge about nutrition by detailed and thoughtful analysis of symptoms of hunger, starvation, and satiety. Its major interest is at the border land of science. Perhaps it might have been called "A Devotion to Starvation," since the author has endured a total of more than 1000 days of complete starvation at one stage or another of his remarkable career as a faster. Certainly much more is learned from this approach to the problem than the publicized self-imposed starvation of Gandhi or the long-forgotten Mayor of Cork. It still falls short of the trained objectivity of a scientific work.

WILLIAM B. BEAN, M.D.

Subacute Bacterial Endocarditis. By Andrew Kerr Jr., M.D. Price $6.50. Pp. 343, with 7 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill. 1955.

Although in the last fifteen years the patter of the clinical puzzles presented by patients with febrile illness—fever of unexplained origin—has shifted away from infectious diseases toward neoplasms, lymphomas, leukemias, and collagen disorders, subacute bacterial endocarditis remains a challenging problem diagnostically, therapeutically, and in terms of pathogenesis. Here, more than in most diseases, experience is likely to be critical element in

reaching a proper diagnosis soon enough to provide appropriate therapy. Kerr's book, which is a repository of the distilled clinical experience in the last seventy-five years, presents a thoughtful discussion of the complicated clinical problems and a comprehensive survey of the evolution of medical thought about bacterial endocarditis as it emerged from a rather confused connection with rheumatic fever to achieve respectable autonomy as an independent disease.

Subacute bacterial endocarditis has no one sign pathognomonic in and of itself. There are many clues which in the aggregate lead the physician to the proper diagnosis. This is of urgent importance because in any given case the later the diagnosis is made and therapy is started the less chance there is for recovery, or "recovery" without a crippled heart. To those who remember when the diagnosis of subacute bacterial endocarditis was the signal and seal of doom and the advances through the short sulfonamide era into the antibiotic period of today, Kerr's book rehearses the step-by-step progress in our understanding of the disease. For younger physicians who do not recall these stages, the book gives a graphic and glowing account of emergence of bacterial endocarditis from a "malignant" and "fatal" disease to a disease formidable rather than necessarily fatal. Among the notable features of the book are an excellent index, including an author index, and an extremely thorough bibliography which enables one to check original sources very readily. Reading, as I often do, with one finger in the index and a thumb in the bibliography, I find moving back and forth in this book much easier than in many. The only reference I looked for without finding was to Ruegsegger's classic studies on pneumococcic endocarditis, but this is really an acute, not subacute endocarditis. When confronted with a case of probable or proved bacterial endocarditis, we frequently ask ourselves what is the incidence or frequency of this or that sign or symptom. Memory being what it is, few of us keep such details in reach of ready recall. Having Kerr's book at hand for reference enables one to get first-hand information very simply.

As with all helpful clinical books, this one combines wide personal experience with the subject and a comprehension of papers in the field. These traits have become increasingly rare in authors of many contemporary medical books. To this appropriate equipment, Kerr brings a felicitous style which makes reading not only interesting but a pleasure. Typographical errors are rare. This is a book that no practicing internist should be without. Anyone from the most bewildered undergraduate student to the most experienced clinician will find it a valuable book to study.

WILLIAM B. BEAN, M.D.

The Inquisitive Physician: The Life and Times of George Richards Minot, A.B., M.D., D.Sc. By Francis M. Rackemann, M.D. Price, $5. Pp. 288. Harvard University Press, Cambridge 38, Mass., 1956.

Everyone who knew George Richards Minot recognizes that he was a remarkable man. Physicians and others who learn about him from reading this story of his life and times by his close friend and distant relative, Francis Minot Rackemann, will surely agree. Were the Nobel-prize-winning discovery of the liver treatment of pernicious anemia by him and his colleagues his only contribution, some would say this was not sufficient for true greatness; but such was not the case. The reader will find that his studies of many blood and nutritional diseases remain today the definitive investigations; that his consideration of the social, economic, and emotional factors of disease following in the tradition of Francis Weld Peabody was far ahead of his time; and that his contributions to medical education both in theory and in training a host of our present day professors of medicine was perhaps his most important contribution. These are some of the measures of his greatness. Simply rehearsing these would not make this book the fascinating one it is, but we are permitted to learn many of the intimate matters in Minot's heritage and early life which surely influenced his future.

Few can doubt that New England has produced more than its share of intellectual giants, of whom Minot is an outstanding but by no means unique example. Why should this be? Some have held the "brisk" weather accountable. Others have mentioned the sturdy genetic stock. The reader may find other factors which he may believe of equal or even greater importance. Although genetics and weather were important, to me it was Minot's "insatiable curiosity" and imagination which continually pulled him ahead, in spite of ill health. This desire to understand things made him a keen observer of all natural phenomena which came to his perview. Unsolved problems large and small only piqued his inquisitiveness so that he would not let them go, but worried them until he got the best answers he could. Certainly his deep sympathy for sick people led him to undertake the study of pernicious anemia, then fatal, but

it was the tenacious curiosity and therefore careful observations he made which led to the discovery. Just what innate qualities or which circumstances in his surroundings and upbringing developed him into "the inquisitive physician" remains for each reader to decide for himself. The unfolding and growth of an unusual personality is written here with the wealth of detail and keen understanding only a close friend and fellow New Englander could give. We also become intimately acquainted with many of the other great physicians of our time, so many of whom Dr. Rackemann also has known well, and with the growth of teaching and research in this country as a part of each hospital's responsibility.

CHARLES S. DAVIDSON, M.D.

News and Comment

ANNOUNCEMENTS

Forthcoming Annual Sessions of The American College of Physicians.—The 38th Annual Session of The American College of Physicians will be held in Boston, on April 8-12, 1957. The General Chairman will be Richard P. Stetson, M.D., F.A.C.P., 203 Commonwealth Ave., Boston 16; the President, Walter L. Palmer, M.D., F.A.C.P., University of Chicago Department of Medicine, Chicago 37; the Executive Secretary and General Manager, Edward R. Loveland, 4200 Pine St., Philadelphia 4.

The 39th Annual Session will be held in Atlantic City, N. J., on April 28-May 2, 1958. The General Chairman will be James F. Gleason, M.D., F.A.C.P., 7 S. Oxford Ave., Atlantic City, N. J.

Autumn Postgraduate Courses.—The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be as follows: members, $30, nonmembers, $60. Full details of these courses may be obtained through the Executive Offices of The American College of Physicians, 4200 Pine St., Philadelphia 4.

Course No. 1. Recent Advances in Cardiovascular Disease: Mt. Sinai Hospital, New York; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors; Oct. 8-12, 1956.

Course No. 2. Clinical Neurology: Jefferson Medical College of Philadelphia; Bernard J. Alpers, M.D., F.A.C.P., Director; Oct. 15-19, 1956.

Course No. 3. Internal Medicine: Vanderbilt University School of Medicine, Nashville; Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., M.A.C.P., Co-Directors; Oct. 15-19, 1956.

Course No. 4. Recent Advances in Internal Medicine: University of Washington School of Medicine, Seattle; Robert H. Williams, M.D., F.A.C.P., Director; Oct. 22-26, 1956.

Course No. 5. Selected Problems in Internal Medicine: University of Oklahoma School of Medicine, Oklahoma City; Stewart G. Wolf Jr., M.D., F.A.C.P., Director; Nov. 26-30, 1956.

Course No. 6. Gastro-Enterology: University of Pennsylvania Graduate School of Medicine, Philadelphia; Henry L. Bockus, M.D., F.A.C.P., Director; Dec. 3-7, 1956.

Course No. 7. Electrocardiography: University of Utah College of Medicine and Salt Lake County General Hospital, Salt Lake City; Hans H. Hecht, M.D., Director; Dec. 3-8, 1956.

Course No. 8. Pathologic Physiology of the Blood Dyscrasias: Washington University School of Medicine, St. Louis; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D. (Associate), and Edward H. Reinhard, M.D. (Associate), Co-Directors; Feb. 18-22, 1957.

Cushing's Syndrome

A Progressive and Often Fatal Disease

A Review of 100 Cases Seen Between July 1945 and July 1954

Randall G. Sprague, M.D. Raymond V. Randall, M.D.
Robert M. Salassa, M.D. Donald A. Scholz, M.D.
Section of Medicine
James T. Priestley, M.D. Waltman Walters, M.D.
Section of General Surgery
Arthur H. Bulbulian, M.S.
Museum of Hygiene and Medicine

Mayo Clinic and Mayo Foundation

Cushing's syndrome, in its severe form, is a serious condition that impairs survival and is associated with a high degree of morbidity. While its remote causes have not yet been accurately ascertained, it is now well established that the condition is a direct consequence of excessive secretion of steroid hormones by hyperplastic or neoplastic adrenal cortices. No form of medical treatment in our hands has been uniformly effective.

The exhibit consists of (1) a description of the clinical and laboratory features of the syndrome, (2) a review of theories of its pathogenesis and the salient features of its endocrine pathology, (3) the surgical treatment in 100 patients who had either tumors or hyperplasia of the adrenal cortex and (4) data and photographs illustrating results of adrenalectomy or excision of adrenal cortical tumors in patients with Cushing's syndrome.

Clinical Manifestations

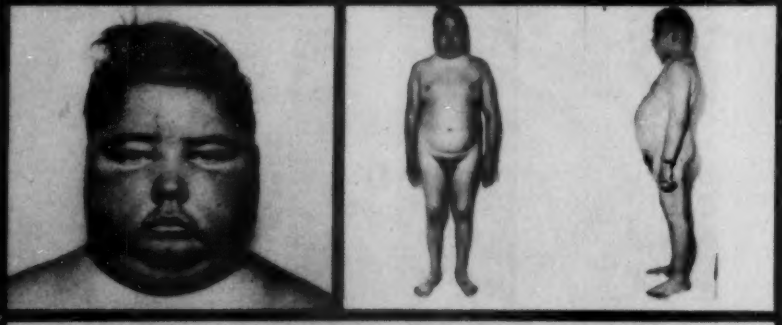
Clinical Signs and Symptoms of Cushing's Syndrome Are Usually Unmistakable

The term "Cushing's syndrome" should be reserved for patients who have most or all of the following physical features: a distinctive habitus characterized by truncal obesity, rounding and plethora of the face, a cervicodorsal hump and relatively thin extremities; thin skin with hirsutism, acne, peculiar purplish striations and a tendency to ecchymosis.

Hypertension, diabetes, osteoporosis, muscular weakness, amenorrhea or loss of libido, and profound psychic changes frequently contribute to the morbidity and mortality of this serious condition.

Cushing's Syndrome in Children

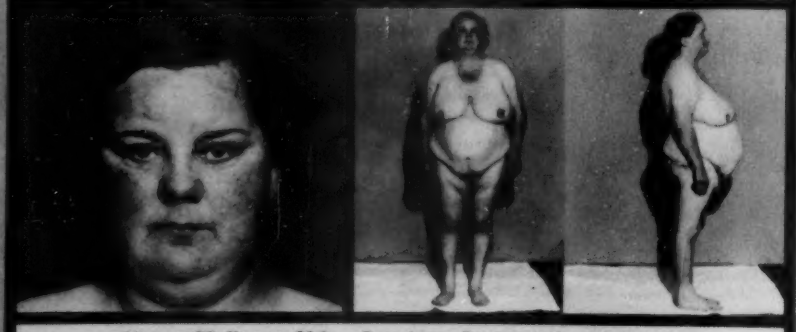
Cushing's syndrome is not common in children; there were 3 in this series. In children less than 10 years of age, it is almost always due to tumor of the adrenal cortex.



Boy 13 Years Old - Symptoms Present for 9 Months

Cushing's Syndrome in Women

Cushing's syndrome occurs most frequently in women. In our series of 100 patients, 80 were females, the peak in age distribution being 30 to 39 years.

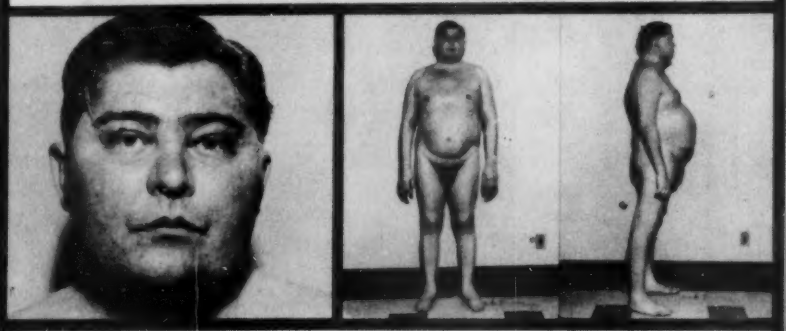


Woman 32 Years Old - Symptoms Present for 6 Years

Clinical Manifestations (Cont.)

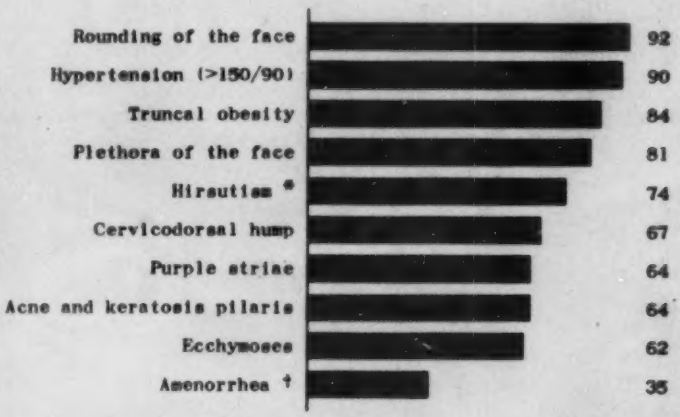
Cushing's Syndrome in Men

Cushing's syndrome occurs less frequently in men. There were 17 men in this series. The age distribution was approximately the same as for the females.



Man 34 Years Old - Symptoms Present for 4 Months

Cushing's Syndrome
Clinical Signs and Symptoms
An Analysis of 100 Cases



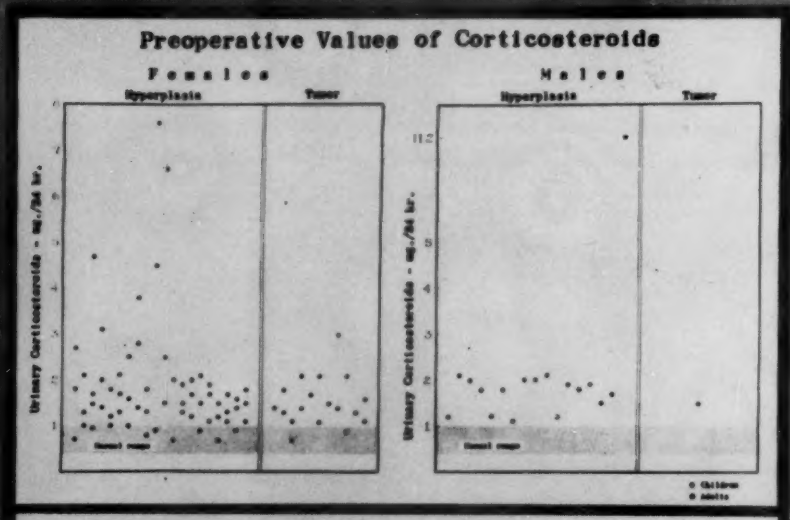
* There were 81 females, including one child.
† There were 63 females between the ages of 29 and 45.

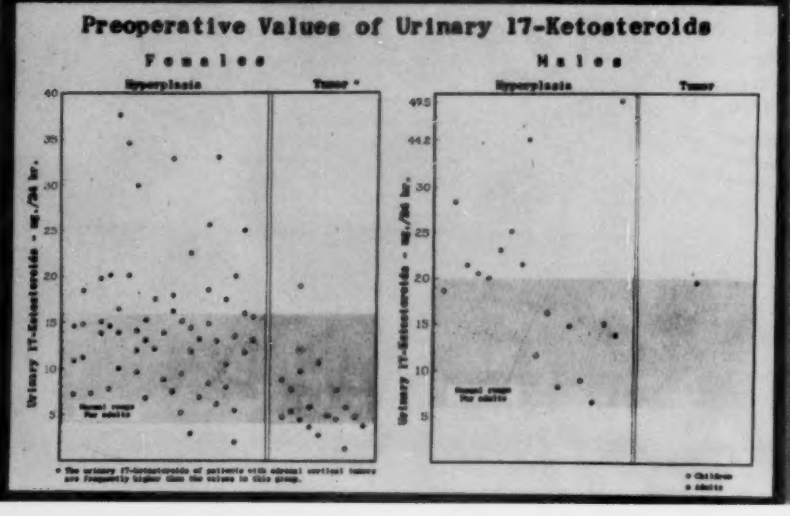
Laboratory and Roentgenologic Findings

Laboratory and Roentgenologic Studies Are Helpful but not Diagnostic

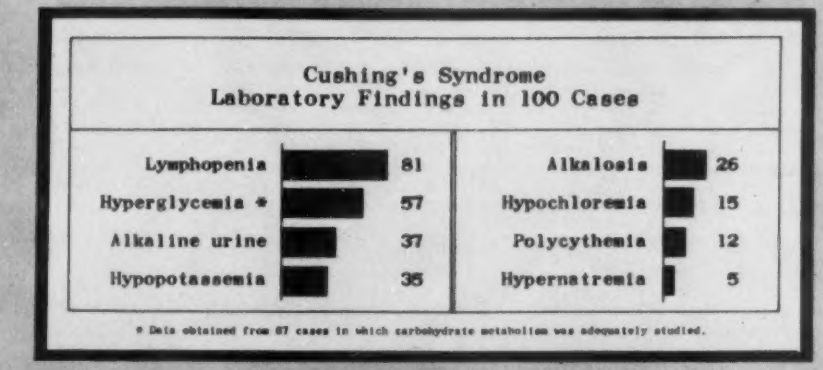
In Cushing's syndrome, urinary 17-ketosteroids vary, depending in part on the type of the adrenal lesion. Urinary corticosteroids and blood 17-hydroxysteroids are usually increased.

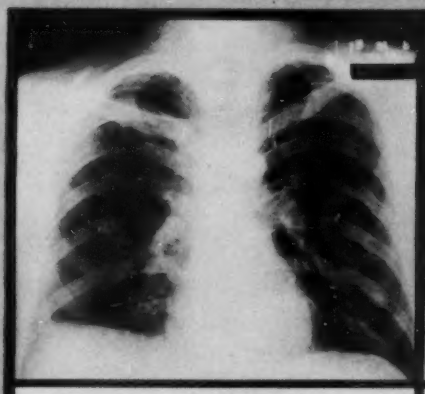
Other laboratory findings may include alkaline urine, lymphopenia, eosinopenia, polycythemia, hyperglycemia and hypochloremic hypopotassemic alkalosis. A frequent roentgenologic manifestation is osteoporosis of the spine, pelvis, skull and other bony structures. Collapse of vertebrae and spontaneous fractures of ribs may occur. Renal calculi or nephrocalcinosis may be present. Rarely is there roentgenologic evidence of a pituitary tumor.





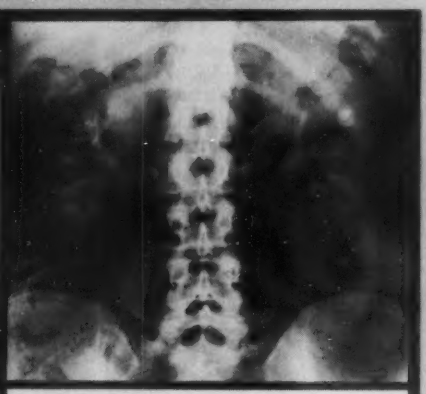
Laboratory and Roentgenologic Findings (Cont.)





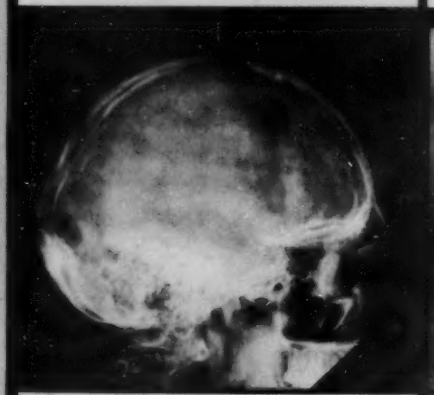
Pathologic Fractures

Pathologic fractures of the ribs secondary to osteoporosis occurred in 20 cases.



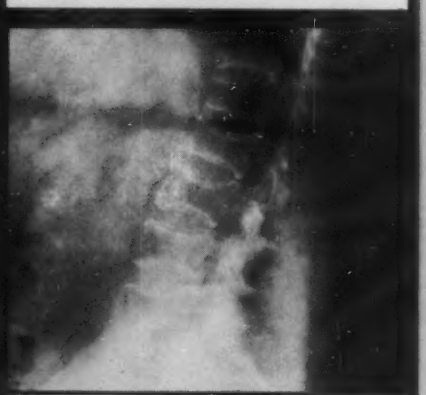
Renal Calculi

Renal calculi were found in 5 cases and nephrocalcinosis in 2 cases.



Pituitary Tumors

Pituitary tumors were demonstrable roentgenologically in 6 cases. Osteoporosis of the skull was seen in 33 cases.



Osteoporosis of Spine

Osteoporosis of the spine was observed in 40 cases; in 17 of these, collapse of one or more vertebrae was present.

Pathology and Pathogenesis

The Immediate Cause of Cushing's Syndrome Is Adrenal Cortical Hyperfunction

Early writings on Cushing's syndrome emphasized the anterior lobe of the pituitary gland as the probable seat of the disorder. Later, the association of the syndrome with hyperplasia or neoplasia of the adrenal cortex suggested a relationship to adrenal cortical hyperfunction. More recently, the proved ability of excessive doses of cortisone, hydrocortisone or corticotropin to induce virtually all of the signs and symptoms has provided impressive evidence that the clinical picture is actually a direct consequence of adrenal cortical hyperfunction. However, the remote cause of the condition remains unknown.

Pathology of the Adrenal Cortex Analysis of 100 Cases

The essential pathologic processes in the adrenal cortex are hyperplasia * and benign or malignant tumors. Both processes may be associated with identical clinical syndromes. Many of the hyperfunctioning tumors are remarkably small, and differentiation between tumor and hyperplasia may not be possible without surgical exploration of the adrenal glands.

* The term "adrenal cortical hyperplasia" is used in this exhibit in a physiologic sense to designate hyperfunctioning adrenal glands that are not the site of tumors. In some cases of frank Cushing's syndrome such adrenal glands are of normal weight and definite cytologic evidence of hyperplasia may be lacking. Multiple small adenomas may be present.

Cortical Hyperplasia

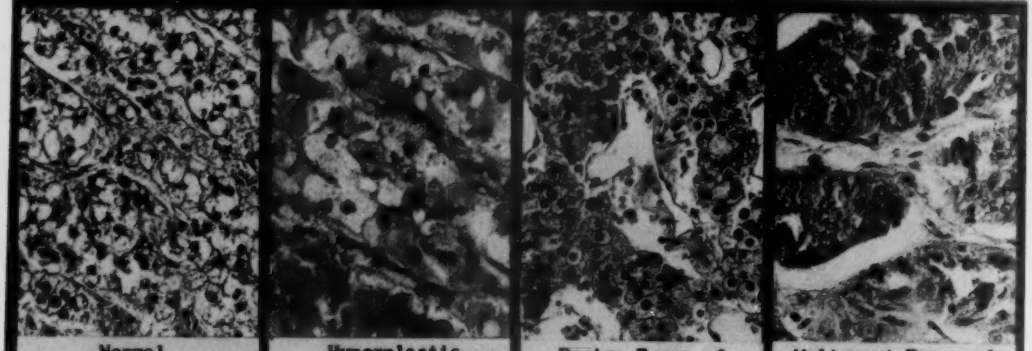
81 Cases
Weight of Totally Removed Single Gland

2.5-6.0 gm. 8 cases | 6.1-8.0 gm. 28 cases | 8.1-10.0 gm. 20 cases | 10.1-12.0 gm. 8 cases | 12.1-26.5 gm. 7 cases

Cortical Tumors

14 Adenomas - 5 Carcinomas
Weight of Tumor

5-10 gm. 3 cases | 11-15 gm. 8 cases | 16-20 gm. 3 cases | 21-30 gm. 3 cases | 31-40 gm. 2 cases



Normal Adrenal Cortex x225 | Hyperplastic Adrenal Cortex x225 | Benign Tumor of Adrenal Cortex x225 | Malignant Tumor of Adrenal Cortex x225

Pathology and Pathogenesis (Cont.)

The Remote Cause of Cushing's Syndrome an Unsolved Problem

It is not known whether Cushing's syndrome, when associated with adrenal hyperplasia, is due to a primary disorder of the anterior lobe of the pituitary gland or to a primary disorder of the adrenal cortex. Basophilic tumors of the pituitary gland, usually microscopic in size, occur in about 50 per cent of cases and Crooke's hyaline change of the nonadenomatous basophilic cells in almost all cases. Current theories of the relation between the changes in the pituitary gland and adrenal hyperplasia are shown below. Present evidence favors the hypothesis that Crooke's changes are a consequence, rather than a cause, of adrenal hyperfunction, and it is possible that basophilic tumors may be similarly related.

Theory of

Pituitary Origin

of Cushing's Syndrome

Cushing's syndrome is due to a primary disorder of the anterior lobe of the pituitary gland. The changes in the pituitary are the cause of adrenal cortical hyperfunction through excretion of excessive amounts of corticotropin.

Theory of

Adrenal Origin

of Cushing's Syndrome

Cushing's syndrome is due to a primary disorder of the adrenal cortices. The changes in the pituitary gland are a consequence, rather than a cause, of adrenal cortical hyperfunction.

Surgical Treatment and Results

Operation on the Adrenal Gland Is the Treatment of Choice

Surgical removal of a hyperfunctioning adrenal cortical tumor or extensive resection of hyperplastic adrenal glands is consistently followed by a remission of the signs and symptoms of Cushing's syndrome. No other treatment in our hands has afforded equally satisfactory results.

All of the 100 patients whose cases form the basis of this exhibit were treated surgically. There were seven hospital deaths, five of these occurring among the early cases before cortisone became available. Considering the poor prognosis of Cushing's syndrome, the surgical mortality is not excessive. Availability of cortisone has greatly facilitated preoperative and postoperative care of these patients.

Woman 36 Years Old
With Cushing's Syndrome (Left)
Appearance of Patient 30 Months Following
Left Subtotal and Right Total
Adrenalectomy (Right)

Woman 32 Years Old
With Cushing's Syndrome (Left)
Appearance of Patient 23 Months Following
Left Subtotal and Right Total
Adrenalectomy (Right)

Woman 24 Years Old
With Cushing's Syndrome (Left)
Appearance of Patient 6 Months Following
Removal of a Low-Grade
Adrenal Cortical Carcinoma
Weighing 10.5 Gm. (Right)

Child 17 Months Old
With Cushing's Syndrome (Left)
Appearance of Patient 9 Months Following
Removal of an Adrenal Cortical Carcinoma
Weighing 35 Gm. (Right)

Surgical Treatment and Results (Cont.)

Boy 13 Years Old
With Cushing's Syndrome (Left)
Appearance of Patient 13 Months Following Left Subtotal and Right Total Adrenalectomy (Right)

Boy 17 Years Old
With Cushing's Syndrome (Left)
Appearance of Patient 12 Months Following Left Subtotal and Right Total Adrenalectomy (Right)

Summary of Results of Surgical Treatment

Of 81 patients treated by adrenalectomy (67 subtotal, 14 total) for adrenal cortical hyperplasia, 63 are currently in remission from 8 months to 9 years (average over 3 years); seven died postoperatively; five died later after satisfactory remission; four are not in full remission. Adequate data are lacking in two patients. Incidence of recurrence to date has been about 10 per cent.

Of 19 patients treated by excision of adrenal cortical tumor, 18 are currently in remission, from 9 months to 8 years (average over 3½ years). One died of metastatic adrenal cortical carcinoma.

Enlarged Adrenal Glands

Frequently, enlarged hyperfunctioning adrenal glands are found. Total adrenalectomy on one side and subtotal (90 per cent) adrenalectomy on the other side is the usual procedure. Occasionally, bilateral total adrenalectomy is performed to insure against recurrence.

Adrenal Glands of Normal Size

Occasionally, hyperfunctioning adrenal glands of normal size may be responsible for Cushing's syndrome. When such is the case, a subtotal (90 per cent) adrenalectomy on one side and total adrenalectomy on the other side, or bilateral total adrenalectomy, should be performed.

Benign Hyperfunctioning Tumor of Adrenal Gland

A benign hyperfunctioning tumor of the adrenal cortex may cause Cushing's syndrome. Such a tumor is removed and the opposite gland, which is atrophic, is preserved. In time, the atrophic gland regains normal function.

Malignant Hyperfunctioning Tumor of Adrenal Gland

A malignant hyperfunctioning tumor of adrenal cortex may cause Cushing's syndrome. Such a tumor is removed and the opposite atrophic gland is preserved. Unless the malignant tumor recurs, the atrophic gland eventually regains normal function.

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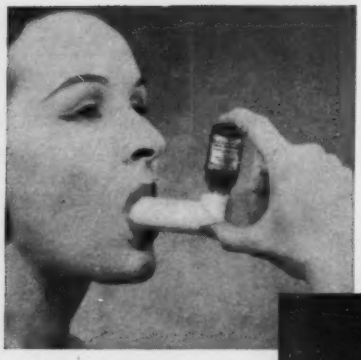

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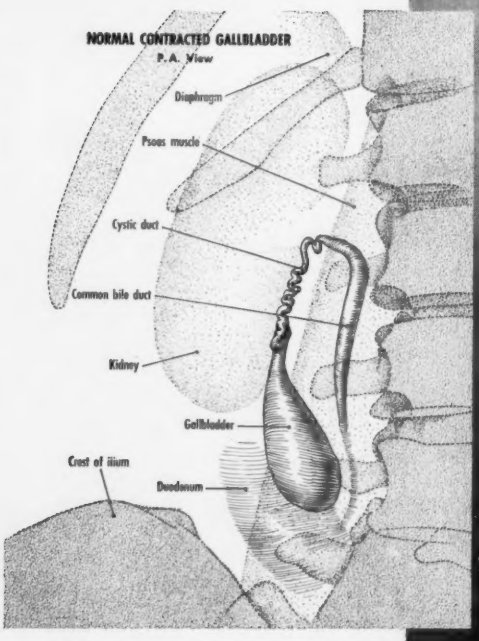

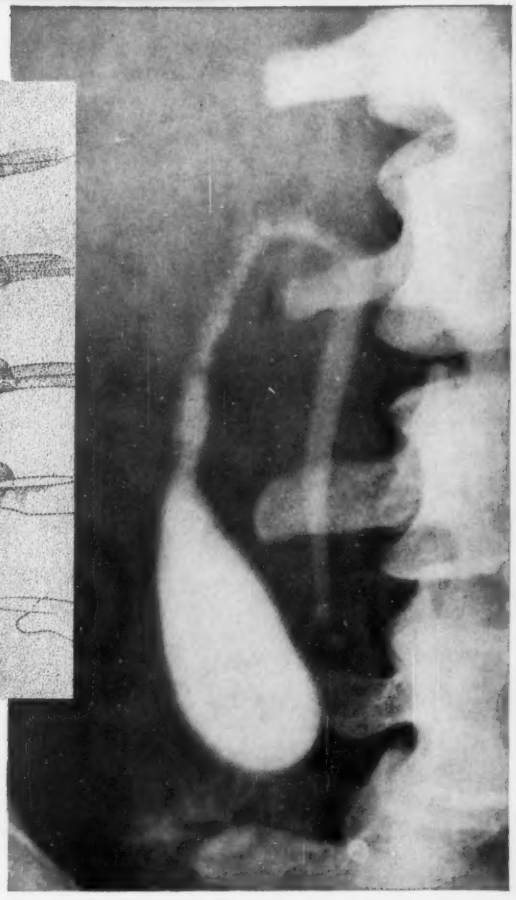

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Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

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